



*American Journal of*  
DIGESTIVE DISEASES  
Volume VII





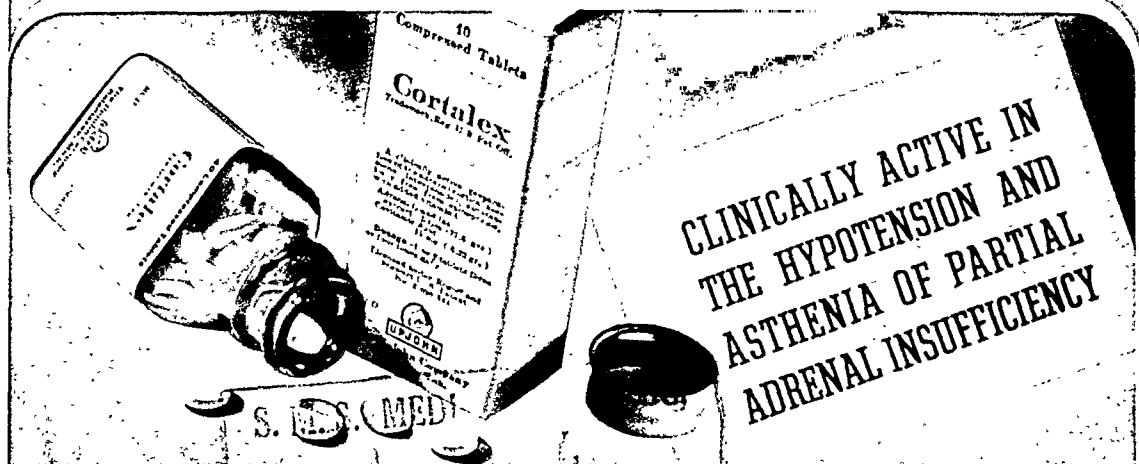
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*The Official Publication of*  
**THE AMERICAN GASTRO-ENTEROLOGICAL ASSOCIATION**

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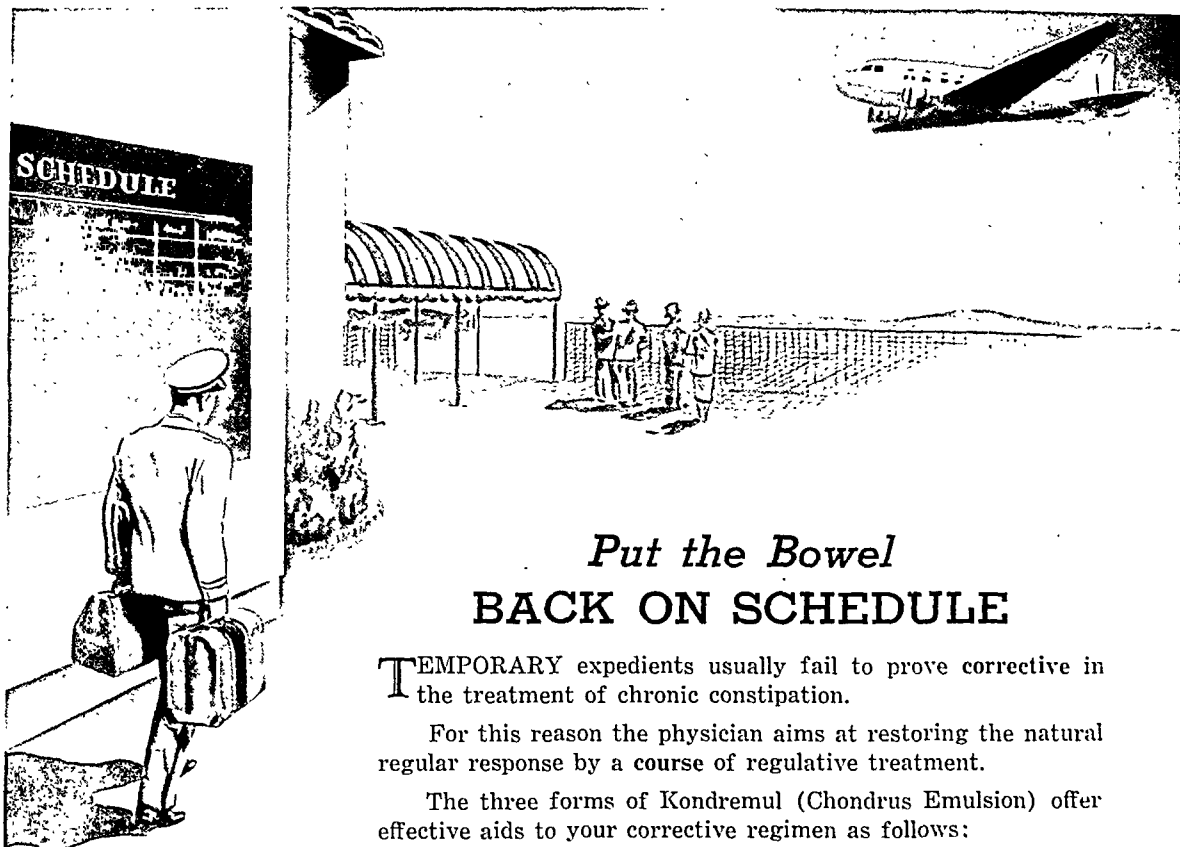
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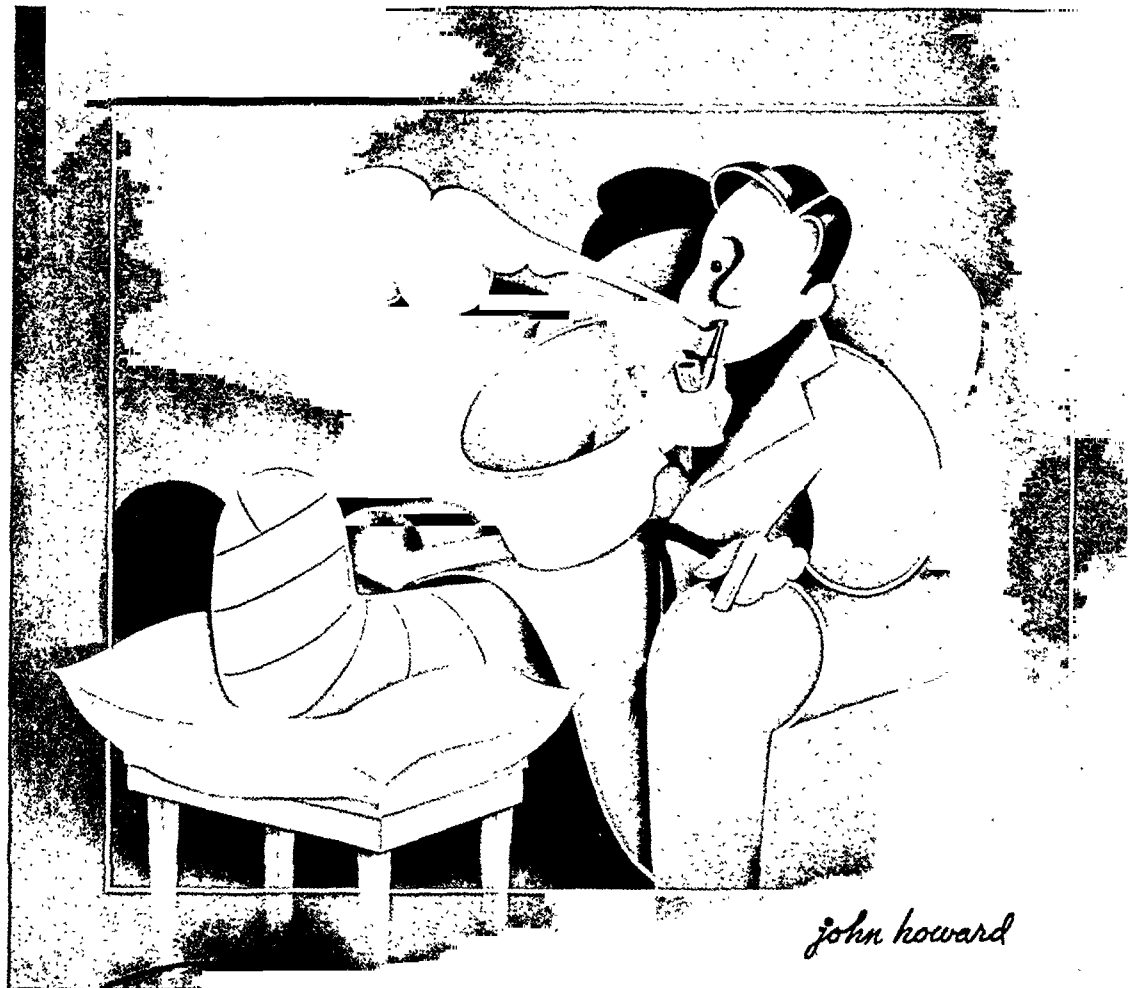
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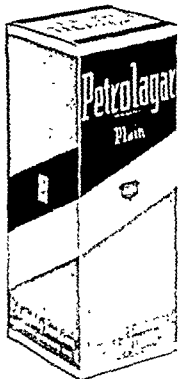




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Clinical investigations have also established the importance of vitamin K in the clotting of human blood (3, 4). It has been demonstrated that avitaminosis K results in a prothrombin deficiency, with resultant prolonged blood clotting time. Although hypoprothrombinemia

can frequently be attributed to inadequate intestinal absorption of vitamin K or to hepatic injury, other causative factors are also recognized; important among these is a deficiency of vitamin K in the diet.

The distribution of vitamin K in foods also has been studied. It has been found that vitamin K activity appears to be concentrated in the photosynthetic portion of the plant (3). Research during the next several years should add greatly to our knowledge of the extent to which this factor occurs in common American foods.

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1. 1937. Annual Review of Biochemistry, 6, 364.
2. 1939. Ibid. 8, 428.
3. 1939. J. Am. Med. Assoc. 112, 1457.
4. 1939. Ibid. 113, 2056.

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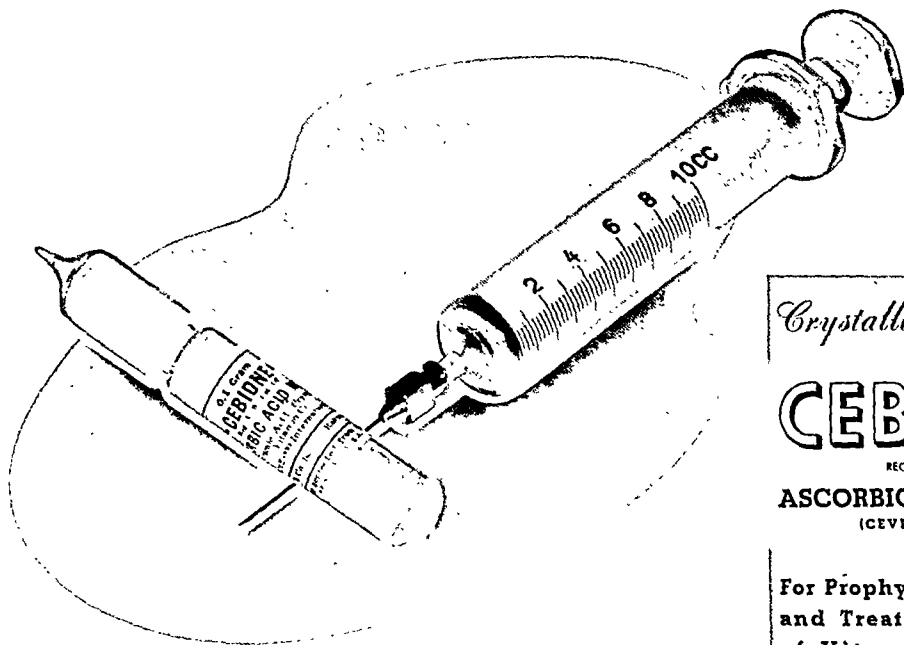
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The graceful, palm-like leaves of the banana plant adapt themselves in interesting fashion to sunshine and shade. When sun rays are intense, the blades collapse and pores on the undersurfaces contract, protecting the plant against too great evaporation.

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## — Logical Dietetics —

**E**RRORS in dietetics arise when there is a failure to separate the several distinct purposes to be attained by specific measures. Mistakes may be avoided by setting up clearly the objectives of the diet. In brief, these are;

1. Mechanical consistency, such as: rough or smooth, bulky or concentrated, lean or fatty, hard or soft.
2. Chemical constitution, such as: its carbohydrate, fat and protein content, vitamin and mineral content, tendency for allergic reactions, and caloric value.

3. The cleanliness and appetite arousing and satisfying value must also be considered.

People with gastro-intestinal symptoms require smooth, concentrated, soft, bland foods and adequate amounts of vitamins and minerals. The food should be appetizing and yet must satisfy the patient so as to enhance his desire to adhere to the diet.

The banana fulfills these requirements and is a useful food for the majority of diets used in treating gastro-intestinal disease.

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#### TABLETS

LITERATURE AND  
ADDITIONAL INDICA-  
TIONS UPON REQUEST

Trasentin\*\* (hydrochloride of diphenyl-acetyl-diethylamino-ethanol) allays both neurogenic and myogenic spasms of many smooth muscles. Rapid absorption assures quick action in relieving spasms of G.I. tract, biliary tract, genito-urinary tract.

\*Johnson, J. R. & Reynolds, S. R. M., *Jl. Pharm. and Exp. Therap.*, April, 1937.  
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\*\*Trade Mark Reg. U. S. Pat. Off. Word "Trasentin" identifies the product as hydrochloride of diphenyl-acetyl-diethylamino-ethanol of Ciba's manufacture.



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# Dilatation of the Bile Ducts and Its Relation to Distress After Cholecystectomy\*

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MANY patients note distress in the upper part of the abdomen or gaseous indigestion after cholecystectomy, even if there is no lesion affecting the duct such as stone or stricture. This distress is usually insignificant but occasionally it constitutes a serious problem. Since Westphal and others have developed the concept of motor dysfunction of the biliary tract, this study was undertaken to find anatomic evidence of motor dysfunction after cholecystectomy, and correlation of this with distress after cholecystectomy.

One hundred and seventy-five consecutive cases were studied at necropsy to establish normal measurements of the extrahepatic bile ducts, and to note any change in the ducts in the presence of abdominal disease, especially of the gall bladder.

Forty-seven cases could be considered as normal: there had been no abdominal symptoms and there was no postmortem evidence of abdominal disease. The

cholesterosis without stones, mild cholecystitis without stones, and stone with normal mucosa were classed as mild gall bladder disease. Cholecystitis with stones, obstructed cystic duct, empyema of the gall bladder, and contracted gall bladder were classed as severe gall bladder disease. Table I gives the measurements in the different groups.

It may be seen that dilatation of the common duct is roughly proportional to the disease of the gall bladder wall. Bollman, Mann and DePage showed in experimental cholecystitis that loss of concentrating power is proportional to the damage to the gall bladder wall. As the gall bladder loses its power to reduce the volume of bile in the duct system by absorption of water and chlorides, the pressure in the system rises until either the secretory pressure of the liver is reached or the resistance of the choledochal sphincter is overcome. This increase in pressure in the duct system causes dilatation of the ducts.

Subjects coming to necropsy months or years after cholecystectomy were studied to determine the re-

TABLE I

*Circumference of common bile ducts of normal persons and of patients who had various abdominal diseases*

Physical Condition	Number	Circumference Common Duct, Average, mm.	Per Cent Greater Than Normal
Normal	47	12.3	0
Peptic ulcer and carcinoma of stomach	18	12.0	0
General peritonitis	16	11.9	0
Miscellaneous abdominal disease	40	12.2	0
Gall bladder disease, mild	27	16.2	32
Gall bladder disease, severe	27	20.2	64

internal circumference of the common duct varied from 9 to 20 mm., with an average of 12.3 mm. The figures given in the standard textbooks of anatomy fall within this range.

Eighteen cases of peptic ulcer and gastric carcinoma and sixteen cases of general peritonitis showed no dilatation of the bile ducts.

Forty cases with various intra-abdominal diseases such as ancient appendicitis, carcinoma of the bowel, and so forth showed no dilatation of the bile ducts.

In fifty-four cases there was disease of the gall bladder without history or postmortem evidence suggesting stone in the common duct. Cholesterol polyps,

TABLE II  
*Postoperative abdominal symptoms*

	Number of Cases	Normal Ducts		Dilated Ducts	
		Number	Per Cent	Number	Per Cent
Epigastric distress gaseous indigestion, postcholecystectomy colic	14	2	14	12	86
No postoperative abdominal symptoms	18	15	83	3	17

lationship of dilatation of the ducts to postcholecystectomy distress. Cases were selected in which a systematic history had been taken since cholecystectomy, in which there was no evidence of stone in the common duct, in which the common duct had not been opened or injured surgically, and in which there had not been a complicating disease that would confuse symptoms. The findings are given in Table II.

The correlation between distress after cholecystectomy and dilatation of the common duct is striking. It has been shown in animals that there is an increase in pressure in the duct system after cholecystectomy. Butsch, McGowan and Walters have shown that spontaneous or induced rise in intraductal pressure is associated with pain. In any hollow muscular viscus, increased internal pressure will eventually cause dilatation, and a sudden increase in pressure will cause pain. Loss of the absorptive, pressure-regulating

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function of the gall bladder produces both dilatation of the ducts and discomfort or pain.

Some patients have neither distress nor dilatation of the ducts after cholecystectomy. This is probably due to variation in the resistance offered by the choledochal sphincter. If the disease process in the gall bladder wall has progressed gradually the sphincter of Oddi may have been able to adjust and finally reach the state of species without gall bladders, having almost no sphincter resistance.

Two patients had distress after cholecystectomy but showed no dilatation of the ducts at necropsy. After a period of distress the sphincter may have lost its tone, and the duct wall retained enough resiliency to return to normal. Distress is most frequent in the weeks and months following operation.

Three patients had had no distress after operation but at necropsy the bile ducts were dilated. The distress may have been so insignificant that it was forgotten, or the individuals may have had a low sensitivity to pain.

The association of pain with the slight dilatation after cholecystectomy is in contrast to the absence of pain in association with the huge dilatation of the bile ducts with carcinomatous obstruction. In complete obstruction intraductal pressure equals the secretory pressure of the liver and remains constant. After cholecystectomy intraductal pressure varies widely from one moment to the next depending on the state of the choledochal sphincter. Rapid change in tension of smooth muscle fibers constitutes the adequate stimulus for production of visceral pain.

### REPORT OF CASES

The following case is presented as an example of mild distress after cholecystectomy:

*Case 1.* A man, aged forty-three years, was admitted to The Mayo Clinic in 1909, complaining of recurrent attacks of colicky pain under the right costal margin, with associated nausea but without jaundice. There was residual tenderness after attacks.

Cholecystectomy was performed. The common duct was not explored. The pathologic report was chronic cholecystitis with stones.

For two and a half years after operation the patient noted discomfort in the region of the gall bladder and occasional colic suggestive of the preoperative colic but less severe.

The patient's final admission was in 1926 when his death was caused by acute glomerular nephritis. At necropsy the stomach, duodenum, pancreas and liver were normal. The common duct was dilated grade 1+ on the basis of 1 to 4.

The next case was not included in the statistical study because of repeated choledochostomies, but is presented as an example of the fortunately rare cases of intractable distress after cholecystectomy.

*Case 2.* A woman, aged forty-three years, in 1928, began having attacks of colicky pain under the right costal margin. Cholecystectomy was done elsewhere in 1930; the pathologic diagnosis was strawberry gall bladder without stones. The patient did well until 1932 when she began having severe pressing pain in the right upper quadrant of the abdomen, extending through to the back. Attacks of such pain continued.

In 1934 at The Mayo Clinic the common bile duct was explored and no abnormalities found. A T tube was left in the common duct for eight months. There was no pain as long as the tube drained freely. After removal of the

tube the pain recurred, more frequently and severely than before. In October, 1935, the right splanchnic nerve, the trunk from the twelfth dorsal ganglion, and a portion of the celiac ganglion were resected. Pain was relieved for a period of two months.

In June, 1936, the common duct was explored, the choledochal sphincter dilated with scopes, and a T tube left in the common duct. Three weeks later the T tube came out spontaneously with recurrence of pain.

In September, 1936, the left major splanchnic nerve and its branches and a portion of the celiac ganglion were removed, relieving pain for four weeks.

In December, 1936, a T tube was placed in the common duct. As the stomach and duodenum were markedly dilated, a duodenojejunostomy was done. The patient was comfortable thereafter unless the T tube was clamped. In September, 1937, she died following an attempted hepaticoduodenostomy.

There was no dilatation of the ducts at necropsy. Microscopic examination of the choledochal sphincter showed the muscle fibers enlarged a third to a half.

This patient was comfortable only when there was a T tube in the common duct, relieving the pressure in the duct system. Enlargement of the muscle fibers of the choledochal sphincter has been noted in cases of biliary dyskinesia by Westphal, after cholecystectomy by Nuboer, by Westphal and by Mann, and in experimental cholecystitis by Mann. Hypertrophy of the muscle fibers, and perhaps irritability of the normal mechanism producing contraction of the choledochal sphincter, account for the severity of symptoms in this case.

The splanchnic nerves are the accepted pathway for pain impulses from the common bile duct. In this case section of the splanchnic nerves gave only temporary relief.

This patient occasionally suffered pain when the T tube in the common duct was draining freely. In some cases pain can be duplicated by increasing pressure within the second portion of the duodenum. After the duodenojejunostomy, opening the T tube always relieved this patient.

### CONCLUSIONS

Normal measurements of the circumference of the extrahepatic bile ducts were established.

These measurements were not altered by peptic ulcer, gastric carcinoma or general peritonitis.

There was dilatation of the extrahepatic ducts in the presence of disease of the gall bladder wall, roughly in proportion to the severity of disease.

Distress after cholecystectomy is closely related to dilatation of the bile ducts after cholecystectomy, both being due to loss of the absorptive function of the gall bladder and rise in pressure within the duct system.

In one case of severe distress after cholecystectomy the circular fibers of the choledochal sphincter showed marked hypertrophy.

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# The Comparative Value of Serial Hippuric Acid Excretion, Total Cholesterol, Cholesterol Ester and Phospho-lipid Tests in Diseases of the Liver\*

## II. A Clinical Comparison of the Tests

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IN the previous paper an attempt was made to obtain a better understanding of the condition of the liver during various diseases by means of a number of liver function tests. The methods used were described and the results presented in detail. In this paper the clinical application of these various tests in diagnosis and prognosis will be compared.

In discussing our results we wish to mention several general factors in the use and comparative value of liver function tests which are well recognized by those who are familiar with them, but not always by the profession at large which tends to expect too much of them.

Liver function tests may be used in various ways:

1. To detect the presence and amount of liver damage and to follow the changes and course in an attack of jaundice.
2. For prognosis during the attack to assist in the decision concerning surgical risk and to discover the amount of residual liver damage after the attack is over.
3. For differential diagnosis.

The objective may be an elaborate biochemical study of liver function in different diseases, or the development of a group of simple tests for routine use in medical or surgical cases of jaundice. It is fair to look critically at these tests and ask if they really add anything to the general clinical picture and tell more about *prognosis* than the patient's symptoms and appearance, i.e. the change in the jaundice, the color of the stools or the course of the icteric index.

Since no one test is entirely satisfactory, it is better to use several, testing several types of functions such as excretion and some type of metabolism. In testing several functions of the liver, one positive test is almost as good a sign of liver damage as if all were positive, but there is usually a correlation between the amount of injury to the liver and the number of different kinds of tests which show abnormalities.

The different effect of a given disease of the liver on its various functions and their tests is shown on the tables and charts given in Part 1 of this paper. In Part 2 an attempt is made to evaluate the results and relative usefulness of the various liver function tests which have been presented in the complex problems presented by liver disease.

**Prognosis:** From the standpoint of prognosis, the phospho-lipids and total cholesterol values in the blood have given us very little information of value. In one

fatal case of portal cirrhosis (Case 31)\* there was a progressive change from high to low normal range over a period of 1½ months, whereas a definitely bad prognosis was indicated by both hippuric acid and bromsulphthalein tests.

The *cholesterol ester percentage* has definite prognostic value in acute liver diseases such as acute hepatitis (catarrhal jaundice, acute yellow atrophy and toxic hepatitis). Falling values and a very low figure are serious signs and a high figure shows a mild disturbance. Progressive improvement from low to normal figures is seen in the more severe cases of acute hepatitis which recovered (such as Cases 2, 7, 8, 11 and 13). The ester percentage has disclosed very little information of prognostic value in the chronic cases and has been normal in about half of the fatal cases. In one case of portal cirrhosis, (Case 31), the ester percentage rose steadily over a period of six weeks, ending at normal just before death. In an additional case of fatal extensive primary carcinoma of the liver developing upon portal cirrhosis, three-fourths of the liver was found to be necrotic cancer at autopsy and the remainder showed portal cirrhosis. The ester percentage within a week of death was only moderately below normal, (50 per cent and 48 per cent) while the hippuric acid values were 1.23, 0 and 0.56 gms.

In one patient with portal cirrhosis (Case 33) who had been jaundiced for a year, the ester percentage was just below normal, while the hippuric acid value was very low.

In the group of cirrheses less than half showed a low ester percentage while all showed low hippuric acid excretion.

The *hippuric acid excretion test* has been helpful in prognosis since it invariably gave low results in all severe and fatal cases. In our experience it has proved more sensitive than the ester ratio in all classes of liver disease. This is most striking in the small group of tumors, all three of which showed a normal ester ratio and a low hippuric acid excretion. This test is valuable in discovering residual liver damage after the jaundice has disappeared or in ruling out liver damage in chronic cases. In this respect it is almost exactly like the bromsulphthalein test.

The hippuric acid excretion test has also assisted in assessing the surgical risk. In cases of gall bladder disease and its complications the post-operative course was favorable when the hippuric acid excretion was between 2.5-3.6 gms. before operation (Cases 55, 58, 60 and 64). On the other hand when the hippuric acid

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\*The Case numbers refer to the tables in Part 1 of this paper, pages 606 to 608 of this Journal, Nov., 1939.

excretion was between 1 and 1½ gms. before operation as in Cases 47, 54, 55 and 56 the convalescence was long and stormy.

With the exception of cases of nephritis and dehydration the hippuric acid test has almost always seemed to reflect the functional capacity of the liver. The test is simple, relatively specific and can be used in jaundiced patients (where the dye test is unsatisfactory). It can usually be correlated with the severity of the lesion as determined either by the clinical course or the amount of liver damage found at operation (biopsy) or necropsy.

Since we have discussed the comparative merits of the hippuric acid test with the other liver function tests and the correlation of this test with the degrees of hepatic damage as revealed by operation or autopsy, we should like to present some exceptions also. We have looked over our series for a badly damaged liver with a hippuric acid test which remained normal, without finding a single one. A repeatedly normal hippuric acid excretion was found in a few cases of liver disease in our series, in which the liver damage appeared to be mild. These were represented by two mild cases of infectious hepatitis with complete recovery within a week (Cases 15 and 17), one patient with stones in the gall bladder without obstruction (Case 52), one case of cancer of the head of the pancreas, with jaundice of only two weeks' duration (Case 49) and one case of partial obstruction of the common duct due to adhesions (Case 52).

On the other hand we have observed a few cases in which the hippuric acid excretion was decreased below normal where there were good reasons for believing that this depression was due, in part at least, to dehydration or poor renal function (Cases 4, 12 and 18).

In 22 cases in the series *bromsulphthalein* tests were made after the jaundice had disappeared. The results of the *bromsulphthalein* and hippuric acid tests were almost identical. In one case of stricture of the common duct (Case 47) the hippuric acid test seemed slightly less sensitive and returned to normal first.

The *Ivy bleeding time* was done in 27 cases and the results agree with Ivy's opinion that a prolonged bleeding time by this method is associated with poor liver function and is a serious prognostic sign. In seven fatal cases in which the *Ivy* test was made, five had prolonged bleeding time (4, 4, 4, 6 and 20 minutes). In a few recent cases the prothrombin time in the blood has been determined in place of bleeding time.

**Differential diagnosis.** Differential diagnosis in the jaundiced patient is undoubtedly the most important of the problems which confront the clinician, yet it is in this particular field that the available tests are least satisfactory. Reliance must be placed upon a group picture rather than on the results of a specific test. In certain instances typical patterns are found and when present are quite reliable. When the picture approaches the borderline between various conditions the diagnosis cannot be made with certainty.

From an examination of our cases, we find that the *phospho-lipids* and *total cholesterol* are consistently high in cases of external obstruction but may also be elevated in toxic hepatitis. The latter can usually be ruled out by a history of exposure to arsenic, cinchon, chloroform, carbon tetrachloride or other toxic substances. Several times in jaundiced patients with

known gall stones or suspected obstruction (Cases 14, 54 and 58) persistently normal phospholipids and total cholesterol have favored the absence of obstruction. Operation was deferred, the diagnosis was confirmed by the course of the illness and the operation performed later when the patient was a much better operative risk.

The *cholesterol ester percentage* has been much less delicate than the hippuric acid test in the diagnosis of the presence of liver injury. In nearly 75 per cent of the acute cases the ester percentage was low, but it was disturbed in only about 50 per cent of the chronic cases such as cirrhosis and gall bladder disease, even in the presence of jaundice.

It is of special interest to compare the results of the ester percentage in acute hepatitis and chronic obstruction which has been considered of value in differential diagnosis by others. Our group of obstructive cases is small but we have found no differential diagnostic value in the ester percentage thus far in these two groups of cases. Both have shown approximately the same percentage normal and the same percentage low at some period of the disease.

It has been a disappointment to find so little differential diagnostic value in the ester percentage in these groups and we have looked for the reason for the difference between our results and those of Epstein and of Shay. It does not seem likely to be a slight difference in the method of analysis or because of the longer duration of jaundice in our obstruction cases but may be due in part to the fact that they place the lower limit of a normal ester percentage at 50 instead of 60 as we have done. We see little difference in our group whether the jaundice and obstruction lasted several weeks or months. The cases of short duration had an ester ratio of 17-53 per cent and the long ones from 11-55 per cent; four-fifths of the group were below 60 per cent which we considered the normal value.

Our group of unselected cases of obstruction included many serious cases, of the kind frequently found in medical wards. Seven of the patients showed carcinoma, five of which died in the hospital, three of the deaths following operation. The cholesterol ester percentage was very low in three, 11 per cent, 17 per cent and 23 per cent; slightly below normal in two, 53 per cent and 55 per cent; and normal in only one, 68 per cent. In one it was low but improved following operation, rising from 33 per cent to 48 per cent.

In one benign stricture of the common duct the ester percentage was normal (71 per cent) and in another rose from low to normal after operation (from 42 per cent to 68 per cent). In two cases of common duct stones the results were just below normal, 50 per cent and 56 per cent.

The ester percentage showed some contrast between the acute and chronic cases. In acute hepatitis nearly 75 per cent were low at some time during the illness and in chronic cases, such as the cirrhoses and gall bladders (with jaundice) less than 50 per cent were low. In the small group of tumors all had a normal ester per cent. These facts have no definite diagnostic value.

The *urobilinogen test* in the urine by showing complete absence had more definite value than the total cholesterol or phospho-lipids in the diagnosis of com-

plete obstruction.\* In the convalescent period after acute hepatitis we have noticed that brown stools often appear several days before the height of the urobilinogen excretion in the urine appeared. This may be because the amount of bile pigments in the bowel must reach a certain level before enough urobilinogen is formed there to overload the liver metabolism and cause it to appear in the urine. Sparkman in estimating approximate quantities of urobilinogen in both stools and urine in such cases noted that the urobilinogen appeared first in the stools and shortly after in large increases in the urine.

The *hippuric acid test* had no differential value in our group of cases since it was positive in all types of liver disease. A few cases with high blood non-protein nitrogen values are detailed for correlation with hippuric acid values.

Case 12—with a blood urea nitrogen of 86 mgm. per cent had an acute biliary cirrhosis with septicemia and died of embolic glomerulo-nephritis. The hippuric acid was 0.54 gms.

Case 9—with a non-protein nitrogen of 175 mgm. per cent had a toxic hepatitis, entered in coma, was anuric and died in 4 days. No hippuric acid test was possible.

Case 4—chloroform ingestion, had a non-protein nitrogen successively of 70, 40 and 30 mgm. per cent. The corresponding hippuric acid was 0.71, 2.20 and 3.72 gms.

We are aware of the effect of dehydration on hippuric acid excretion but since the estimation of dehydration would require *serial* observation of the blood chlorides, sodium, potassium, non-protein nitrogen, plasma volume, CO<sub>2</sub> combining power, as well as renal function and concentration tests, this expenditure of effort hardly seemed justifiable.

#### COMMENT

Since there is no universal test of liver function, the skilled physician chooses this or that test much as the surgeon chooses this or that instrument for an operation, some for cases with jaundice and some for those without jaundice, some for their delicacy, some for their reliability, this for diagnosis, that for prognosis and the detection of small degrees of residual damage. These uses are not interchangeable with a given test as a rule, for it is usually impossible to combine great delicacy and differential value in the same test. This has been proved true of the bromsulphthalein test, which is positive in almost every type of liver disease. We have found the same thing true of the hippuric acid test. On the other hand, the less sensitive galactose tolerance test is usually strongly positive in severe acute diffuse liver cell damage and often negative in chronic liver disease and may have greater differential value but far less prognostic value than the first two tests.

The tests are modified not only by the kind of liver disease present but also by its acute or chronic nature, the degree of regeneration which has taken place, the presence of infection and by the amount of glycogen present in the liver. Simple enlargement of the liver does not necessarily mean poor function.

Vigorous regeneration of liver cells in convalescence and in the remission of chronic disease may mask the extent of the damage and explain many normal results with the ester percentage and galactose tolerance tests.

\*The result of the urobilinogen test in a similar series of 80 cases was reported by one of us (F.W.W.) in 1937. Now in a series of 300 cases we have found the results almost identical.

The liver is so important in keeping a uniform blood sugar level that it is quite evident why carbohydrate tests remain normal even in serious chronic liver disease. The cholesterol metabolism seems fairly stable and while it is upset in an acute attack of liver degeneration shows a strong tendency to return to normal. The mechanism of hippuric acid excretion seems to have little reserve and to be easily upset and often very slow to recover.

We have spoken of the *constant change* in liver function during an attack of jaundice and the need for serial tests. This relation of the test to the *period of the disease* is very important. The liver function must be accurately measured every few days in many cases, beginning early if possible, to show acute changes and carried through the attack for one, two or more weeks. Such figures mean much more than tabulation of results of single tests taken at random in different groups of liver diseases.

It may be asked if it is really safe in a severely jaundiced patient to wait for a period of study of ten days to two weeks instead of advising an early exploration to relieve possible obstruction. Our experience has shown that an accurate diagnosis of the cause of the jaundice is very important, that early impressions and diagnosis in the first few days are often reversed and that in general the chance of an accurate diagnosis is greatly improved by a study period and by watching the course of the illness.

It usually does no harm to wait a week or two in an obstructive case in the *absence* of signs of infection or peritoneal involvement and on the other hand, it is not only useless but dangerous to operate upon a patient with acute diffuse liver cell damage during the height of the attack. All the serious errors we have seen have been of this type and usually might have been avoided by a longer study of the course of the disease and the progressive changes in liver function. Middle-aged jaundiced patients with cirrhosis or acute hepatitis are often admitted to the surgical services with the diagnosis of obstructive jaundice. If a correct diagnosis is not made these patients may come to operation with fatal results.

The importance of this point is seen when we remember that the operative mortality in gall bladder cases varies from 2-5 per cent, in cirrhosis is about 30 per cent and in severe acute hepatitis at the height of the attack almost 100 per cent. Even the patient with proven gall stones in whom the attack of jaundice can be proved to be non-obstructive and largely due to hepato-cellular damage will prove a far better surgical risk when the jaundice has decreased or disappeared and the liver function has improved or returned to normal.

The state of the liver is certainly as important a factor in surgical risk as is the condition of the heart, kidneys or lungs and can often be definitely discovered and followed by sensitive liver function tests.

From our studies we believe that these liver function tests are useful and add information to the general estimate of the patient's condition obtained from the history, physical examination and examination of the urine and stools. They aid both in diagnosis and prognosis but in quite different degrees with the several tests and the different diseases and are of more value in prognosis than in diagnosis. They are hardly needed in the simpler cases such as mild catarrhal jaundice

but have more value in the deep or painless jaundice of middle life.

In two patients of the same age with the same degree of jaundice and a somewhat similar history, some tests may show that one patient is going steadily downhill to death and the other returning to health. The laboratory tests have rarely confused the issue; they have nearly always proved helpful. They may simply parallel the icteric index and the general condition and be needless, but they have often been more definite and accurate than these in discovering liver damage and following its course and in deciding questions of prognosis, residual damage, surgical risk or the urgent need of protective treatment of the liver.

In connection with the hippuric acid excretion test there are certain factors which should be remembered. The test was originally introduced as an index of renal function and evidence has been presented from animal experiments that its synthesis can occur despite severe liver damage or even in total hepatectomy. Nevertheless in clinical experience this test parallels with remarkable fidelity the degree of liver damage in patients with normal renal function. It seems desirable to use the hippuric acid excretion as a test of liver function only when the blood urea nitrogen is approximately normal and obvious non-hepatic causes of dehydration and oliguria such as vomiting, diarrhea or low fluid intake can be excluded.

There is possibly another or contributory factor in the low hippuric acid excretion in acute or subacute disease of the liver. Jones has recently pointed out that oliguria preceding anuria is an important, unfavorable prognostic sign in liver disease and spontaneous diuresis a good sign. The anuria may be associated with ascites, general edema or low total protein in the blood. The liver evidently plays an important part in relation to the movement of water in the body. With hepatic damage a sufficient shift of fluids may take place from the blood stream to the tissues and body cavities to produce oliguria or anuria. The low hippuric acid excretion in such cases may be a secondary effect on the kidney due primarily to the liver. With a return of hepatic efficiency the shift of fluids is reversed and moves from the tissue and body cavities to the blood stream and ultimately causes diuresis and more normal hippuric acid excretion.

While we cannot make direct comparisons of the galactose tolerance test with the other tests in this series of cases, since the galactose tolerance test was not often used, we may venture some comparison with previous experience in a similar series of 80 cases. To avoid confusion the test should be compared in acute and chronic cases separately. For diagnosis in the acute cases the galactose tolerance test behaved much like the ester percentage and was usually strongly positive in severe or moderately severe acute hepatitis but in the chronic cases, (cirrhoses, disease of the gall bladder and tumors), both galactose tolerance and ester percentage showed much less change and were normal in a rather large per cent of the cases. For example, the galactose tolerance was normal in about 75 per cent of the cirrhoses and the ester percentage in 55 per cent. Both were normal in nearly all the tumors and in a variable per cent of the obstructive cases, depending on the amount of secondary liver damage.

In the chronic group it is difficult to use either the galactose tolerance or the ester percentage for useful diagnosis, since the cirrhoses, surgical gall bladders and obstructive cases are so much alike. The tests may have some value in a limited but important field, i.e. in distinguishing acute cellular damage from the early stages of obstruction. However, we agree entirely with Snell that there are important difficulties in distinguishing obstructive from hepato-cellular jaundice when both acute and chronic cases are included. The tests may be negative in some of the early obstructive cases but they are also regularly negative in about 75 per cent of the cirrhoses. They are usually positive in acute hepatitis but are also positive in a large percentage of the later obstructions.

In assessing prognosis or in detecting the presence of liver damage the hippuric acid test was far more delicate than the galactose test. While a positive galactose test is strong evidence in favor of liver damage, it may be entirely normal when the hippuric acid excretion is low in serious or even fatal chronic cases. In our experience we have found that the galactose tolerance test has no value whatever in non-jaundiced cases. Snell and McGath report the same experience.

These liver function tests are supplementary methods, they do not make a diagnosis. No test can take the place of clinical knowledge and experience or diagnostic ability but they have aided in discovering the presence of disease of the liver, in following its course, in prognosis, and in estimating surgical risk. This is enough to justify their use without over-stressing their diagnostic values.

## SUMMARY

In certain cases serial tests are needed to discover the trend of disease in the liver, also the degree of liver damage and the amount of compensation that is taking place.

The tests are of the greatest value in prognosis foretelling the course of the disease, the length of life of the patient, the amount of residual damage to the liver, and the risk in case of an operation.

In acute hepatitis a low ester percentage is a bad prognostic sign, a high percentage shows mild damage, and a progressive improvement in the percentage is indicative of recovery.

The hippuric acid test is somewhat more reliable than the ester percentage in prognosis in the cases of acute liver disease and far more reliable in the chronic cases of cirrhosis and gall bladder disease.

In some cases the return to normal liver function may be very slow. First to return to normal is likely to be the icteric index, or ester percentage, and then later the hippuric acid and the bromsulphthalein tests. Hippuric acid excretion in the urine is definitely lowered by dehydration and by poor renal function as well as by diseases of the liver.

The ester percentage is valuable in the case of an acutely sick, vomiting or dehydrated patient, when the hippuric acid test is not applicable.

In differential diagnosis of diseases of the liver the tests have been much less definite. The phospho-lipids and total cholesterol have been consistently high in marked external obstruction. The ester percentage was of little or no reliable value in distinguishing between acute hepatitis and chronic obstruction.

The variation up and down in the results of the tests may help in diagnosis. The readings almost never improve in malignant diseases of the liver or ducts.

The hippuric acid excretion, like the bromsulphthalein test, is not a differential test since it is positive in all types of liver disease. It does not seem possible to combine great delicacy and differential value in the same test. The order of delicacy from low to high is approximately galactose tolerance, ester percentage, hippuric acid excretion and urobilinogen, bromsulphthalein and bilirubin excretion.

The urobilinogen test in the urine was found to be more valuable than any of the other tests in the diagnosis of complete external obstruction.

A study period of from 10 days to 2 weeks is important in most chronic cases in order to make as accurate a diagnosis as possible and avoid needless and dangerous surgery.

In our experience the most useful tests in cases of acute liver disease with jaundice have been the icteric index, hippuric acid excretion, urobilinogen in the urine, cholesterol ester percentage and galactose tolerance.

In the cases of chronic liver disease with jaundice the icteric index, hippuric acid excretion and urobilinogen in the urine are most helpful. The phospholipids and total cholesterol have value in obstructive jaundice.

In case of liver disease without jaundice the most useful tests have been the hippuric acid and bromsulphthalein tests.

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## Symptomatology of Chronic Atrophic Gastritis\*

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UNTIL recent years the diagnosis of gastritis was looked upon askance, and probably rightly so, because the available methods of making that diagnosis could hardly be called satisfactory. With the advent of the gastroscope, however, the direct visualization of the gastric mucosa and the observation of the actual pathology of this disease have made it possible to make this diagnosis with a high degree of accuracy. From this point of view, therefore, gastritis, although described over a century ago by Beaumont, has become

a relatively new disease. It is also apparent that our previous conceptions of symptomatology, based as they were upon inadequate diagnostic methods, must be revised. Our present opportunity to correlate more closely the patient's symptoms with the changes of the gastric mucosa, as viewed gastroscopically, has opened a new field of study.

Considerable progress has already been made in the study of the gastroscopic appearance of the gastritides, particularly by Schindler (16, 17), Gutzeit (7), Henning (8), Moutier (12), Chevallier (3) and others. Saltzman (15), Konjetzny (9, 10) and Faber (5) have

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made valuable contributions from the pathological aspect. However, there has been a surprising paucity of papers dealing with the clinical manifestations of gastritis. Anyone who has seen, gastroscopically, the markedly altered gastric mucosa would be astonished if these changes did not produce symptoms. Schindler, Ortmyer and Renshaw (18) have described the symptomatology of gastritis of the superficial and hypertrophic types. Bank and Renshaw (2) have described the symptoms of chronic superficial gastritis. Very little, however, has been written about the symptoms of atrophic gastritis. It is with this type of gastritis that this paper will be particularly concerned.

The gastroscopic picture of atrophic gastritis is very characteristic (19). The mucosa is thin and pinkish-gray, gray, or greenish-gray in color. The thinning of the mucosa makes possible the visualization of the blood vessels, a finding that is never present in the normal stomach. One can clearly recognize the dark appearing blood vessels in the light mucous membrane. They have the configuration of branches of a tree. The larger vessels are blue in color, and sometimes smaller vessels which are red in color can be seen forming anastomoses between the larger branches. These atrophic changes may be widespread throughout the stomach or more frequently may be localized in patches. They may be combined with superficial changes, reddening of the mucosa, edema and adherent layers of mucus. Superficial gastritis sometimes precedes atrophic gastritis; in such cases the slow development of extensive atrophy will be observed. Recently, histologic checks of gastroscopic pictures have been made on several occasions. Whenever the characteristic gastroscopic picture was seen, biopsy from the stomach wall revealed microscopically definite thinning of the mucosa; disappearance or reduction of the amount of the gastric glands; transformation of the epithelium into the intestinal type with appearance of many goblet cells; extensive interstitial infiltration of the thinned mucosa, sometimes of submucosa and muscularis as well; and in some cases, development of fibrous tissue in the deeper layers. The typical gastroscopic and histologic picture is not found in healthy adults. The senile atrophy described by Aschoff (1) does not develop before the eightieth year. The symptomatology of chronic atrophic gastritis is still more perplexing than that of other forms of gastritis, and this is probably the reason why there are almost no publications on this subject.

We had as our aims (1) to ascertain the symptomatology, if any, that accompanied atrophic gastritis and (2) to determine whether or not these symptoms were found as frequently in other diseases.

One point should be emphasized. The histories of these patients were taken by students, internes, and other members of the staff of the medical and gastro-intestinal services, and *not by the gastroscopist*. We can be assured that there were no preconceived ideas of the symptoms of atrophic gastritis and no leading questions were asked. Therefore, we can regard the symptoms as recorded in the histories as prominent complaints of these patients, complaints that were offered by the patients without urging.

#### UNCOMPLICATED ATROPHIC GASTRITIS

We were able to collect 41 cases with atrophic gastritis and no other demonstrable pathology whom

we will call for practical purposes "uncomplicated" atrophic gastritis. In this group there were 25 women and 16 men, ranging in age from 32 years to 69 years. They could be subdivided as follows:

32 to 39 years—	9 patients
40 to 49 years—	19 patients
50 to 59 years—	6 patients
60 to 69 years—	7 patients

Thus it would appear that this is a disease of middle life. In this series, at least, young subjects were conspicuously absent. On the other hand, we were unable to demonstrate that atrophic gastritis is more frequent in the sixth and seventh decade of life than before. A short time ago we examined, gastroscopically, a man seventy-eight years of age and found that his gastric mucosa looked exactly like that of healthy young people.

#### DIGESTIVE SYMPTOMS

All of the patients in this group complained of digestive symptoms of some type (Table I). This would be expected, because these patients were referred for gastroscopy because of their digestive complaints. It seems possible, however, that atrophic gastritis may be present without gastric symptoms and may be manifested only by the general symptoms to be discussed later.

The duration of symptoms varied greatly, from one month to twenty-five years. The symptoms were prominently periodic, with remissions of relative or complete freedom. Of the twenty-five charts that gave definite information on this question, only four patients stated that their symptoms were continuous.

Every patient complained of some type of epigastric discomfort. This was most commonly termed a dull pain, but was also described as distress, fullness, heaviness, or more rarely as a burning sensation. This discomfort was always located in the epigastrium and in no case did it radiate elsewhere. None of these patients had experienced any severe or sharp pain.

The relation of distress to the taking of food showed considerable variation. In 46 per cent of these patients the distress came on shortly after meals, in 38 per cent one to four hours after meals, and the remainder stated that they might have distress at any time. In contrast to peptic ulcer patients, only two complained of night pain. Moreover, relief from food or alkali was not common, only five patients claiming relief in this manner. It was interesting to note that two of these five patients had achlorhydria. Loss of appetite was a common and distressing symptom. Many of these patients complained of an anorexia that was almost constant and peculiarly distasteful. Nausea was also common, being, with the exception of pain, the most frequent complaint. We could not escape the impression that the anorexia and nausea were extremely disagreeable in this disease. About half of the patients who had nausea also complained of vomiting. Bloating and belching were frequently encountered, the latter being a complaint in slightly more than 50 per cent of the cases.

Three of these patients had experienced hematemesis. One of these patients had an achlorhydria even after histamine, the second showed no free hydrochloric acid after the Ewald meal, but produced twenty-eight units after histamine, and the third pro-

duced eight units after histamine. This last patient was examined gastroscopically three days after his hematemesis and no ulcerating lesion could be found. None of these patients gave a history that could be considered suggestive of peptic ulcer. Roentgenological examinations showed no abnormalities. It seemed reasonably safe, therefore, to conclude that the atrophic gastritis was the cause of the bleeding in these three cases.

About two-thirds of the patients gave a history of

constipation of varying degree. Only one patient gave a history of periods of diarrhea in spite of the fact that one-third of these cases had achlorhydria. In other words, there was an almost complete absence of so-called gastrogenic diarrhea.

### GENERAL SYMPTOMS

(See Table I)

Faber (5) has already contended that gastritis often produces more general and nervous symptoms than

TABLE I  
*Atrophic gastritis*

Digestive Symptoms							General Symptoms						
Case	Type	Epigastric Distress					Head-ache	Vert.	Nervous-ness	Weakness Fatigue	Sore Tongue	Numbness Tingling	Free HCl
		Immed.	Delayed	Naus.	Vom.	Appet.							
1. W.S.	fullness					poor			xx	xxxx			0
2. E.J.	pain					poor			xx	xx			0
3. R.W.	heaviness	x				poor	x	x	x	xx	x		50
4. M.P.	pain	x	x	x									0
5. B.B.	pain			x		fair				xxxx			0
6. A.O.	pain			x	x	poor				xx	x		56
7. F.F.	fullness	x								xx	x	x	34
8. A.C.	pain	x				poor	xx	xx		xx		x	26
9. C.T.	pain	x				poor				xx			0
10. G.R.	pain	x		x		fair			xx	xxx		x	127
11. A.A.	pain		x		x			x		x			0
12. M.E.	pain		x		x	poor			xx	xxx			28
13. A.P.	pain					poor				xx			27
14. J.M.	distress	x		x	x	poor				xx		x	0
15. C.P.	pain		x	x	x	good	x	x		xx	x	x	0
16. M.R.	pain	x		xx		poor				xx			36
17. M.G.	pain		x							xx			0
18. F.M.	distress	x											27
19. A.Z.				xx	xx		xx		x	xx			12
20. J.D.	heaviness	x				good			xx				12
21. I.D.	pain			x		poor				x			0
22. M.M.	pain	x	x			poor				xxx			0
23. M.C.	pain	x		xx	xx	poor				xx			36
24. M.K.	burning	x					x	x			x		13
25. J.J.	heaviness	x	x			good					x		41
26. J.A.	fullness									xx	x		0
27. T.S.	pain			x	x						x	x	0
28. M.H.	pain	x		x					xx				49
29. R.R.	pain	x					xxx	x	xx				
30. J.L.	pain			x	x	poor				xx			26
31. R.S.	burning												65
32. S.S.	pain					good			xx				56
33. E.J.	pain		x	x		poor			xx		x		22
34. A.H.	fullness	x		x					xx				52
35. H.L.				xxx	x					xxx			15
36. H.B.	distress					poor			xx	xxx			26
37. C.S.	pain		x	xx					xx				28
38. J.P.	pain	x		xxx	xx	good	xx		xx	xx		x	24
39. M.S.	pain		x	xx	xx				xx	xx			60
40. A.S.	burning												22
41. M.W.	pain			x		poor			x	xxx			35

local symptoms. Moutier (13) has also expressed the opinion that the symptoms of atrophic gastritis are more those of a general disease of the whole body than those of a localized disease of the stomach. In this series the general manifestations of the disease were much more striking than the digestive symptoms. In fact, we believe that the combination of symptoms to be discussed here must be considered highly suggestive of atrophic gastritis. The general symptoms also were definitely periodic.

The single most outstanding complaint of these patients was a feeling of intense weakness and fatigue. This sensation usually came on in spells, often with no relationship to exertion. A patient might be sitting quietly in a chair and suddenly be overcome by an intense weakness that seemed to make even moving from the chair an insurmountable task. This feeling might last for a few minutes or several hours. At other times this weakness would be less marked or might subside completely. In many of these people even slight exertion brought on marked fatigue. Some became completely unable to work because of this feeling of exhaustion. Others were forced to seek employment of less vigorous nature. The latter happened frequently enough to bring out one point rather definitely: these patients *wanted to work* but were physically unable to withstand laborious types of work. Because of the complaints of nervousness, weakness, fatigue, and the indefinite digestive symptoms presented by the atrophic gastritis patients, it is quite probable that many of these people are unwittingly treated as psychoneurotics. This is a title that they do not deserve. It is true of course that since psychoneurosis is so common, it is only natural that some patients with atrophic gastritis also have a psychoneurosis. It is also true that the psychoneurotic personality will react in an exaggerated manner to any organic disease. The people of this type who had atrophic gastritis did react more markedly, but they did so along exactly the same symptomatic lines. But if a patient suffering from a mere psychoneurosis complained of weakness or fatigue, it was immediately obvious that he wanted to escape either work or some disagreeable situation in the way characteristic for the "flight into the disease." Difficulty in the differential diagnosis of atrophic gastritis and psychoneurosis as the cause of symptoms was encountered in only three of our cases.

The complaints of weakness and fatigue appeared in two-thirds of the histories of these patients. This was in sharp contrast to patients with other benign gastro-intestinal disorders, as we shall see later. We must reiterate that these histories were taken by other members of the gastro-intestinal department, many by students and internes, but nevertheless showed these symptoms which one would not expect from a gastro-intestinal patient. On the other hand, it was shown in quite a few instances that an inexperienced examiner had omitted some important points in the history. For instance, we recently observed a patient who showed a rather marked atrophic gastritis, whose chart made no mention of any general symptoms. When asked what symptoms had led him to seek medical aid, he replied that he had first noticed a gradually increasing weakness and fatigability which had become so pronounced that he was forced to give up his job as a welder. Although this,

from the patient's point of view, was his most important complaint, it was omitted from his history entirely. If these cases were included in our statistics, the incidence of these symptoms would be even higher than the 66 per cent that was actually found.

Many complained of increased nervousness which seemed to be the result of this distressing weakness rather than the forerunner of it. Some attempted to describe this as a "different" type of nervousness, or as an "inexplicable" nervousness.

In most of the patients their appearance and actions bore witness to these disagreeable general symptoms. They appeared to be tired and worn out, slow of action and low in spirit. The facial expression was often sad and melancholic. They frequently exhibited an attitude of defeat, a type of emotional surrender to this disease that seemed to rob them of their usual vitality. Furthermore, in contrast to the psychoneurotic type, they appeared to be truly seriously ill.

We will not try to explain the occurrence of these general symptoms in atrophic gastritis. Several possibilities have to be considered in the future. (1) The atrophic mucosa may produce a toxin which is absorbed by the blood; (2) some unknown substance present in the normal mucosa and preventing the development of general weakness, etc., may be absent in the atrophic mucosa; (3) the utilizing of the food, especially of protein, may be disturbed in the atrophic stomach; v.Tabora in 1904 (Ztschr. klin. Med., 53: 460) has shown that in achylia proteins are insufficiently utilized; (4) the complete absence of gastric acid may inhibit the functions of other organs, especially of the pancreas, which altered function then may be responsible for the general symptoms.

In addition to these very striking general manifestations, another group of symptoms was remarkable. Eight of these patients gave a history of intermittent soreness of the tongue and two patients told of soreness of the mouth. Seven complained of numbness and tingling of the hands or feet (or both hands and feet), and four others had noticed dull pains in the legs. In all, there were sixteen patients who had one or more of these complaints. The similarity of these symptoms to those found in slight combined cord degeneration accompanying pernicious anemia was obvious. None of these patients had a hyperchromic anemia, however, and only two had an appreciable secondary anemia. The average hemoglobin value for the other fourteen cases was 83 per cent. Of the group of sixteen patients only five had achlorhydria after histamine stimulation, and two others had achlorhydria after the Ewald meal. None of this group showed atrophy of the tongue. Moutier (13), however, has reported that smooth tongue may occur in this type of patient with atrophic gastritis and without pernicious anemia. None of these patients showed demonstrable physical signs of neurological damage. The contention that there is a connection between dizziness and stomach disorder may be more than a myth. Seven of these patients complained of dizziness. Headache was also a prominent symptom in seven cases.

#### LABORATORY FINDINGS.

In the great majority of these patients the blood picture was normal or showed only a slight hypo-

chronic anemia. The Wassermann test was negative in all cases. With few exceptions the stools consistently showed an absence of occult blood.

The study of the gastric contents had unexpected results. At one time it was believed that atrophic gastritis was always accompanied by achlorhydria. During recent years, however, numerous cases of distinct atrophic gastritis have been observed in which free hydrochloric acid has been found in the stomach secretion. Our present study not only verifies these observations but shows that the *majority* of patients with atrophic gastritis are able to produce free hydrochloric acid. Gastric analyses were done in forty of the forty-one cases. Of these forty cases, free hydrochloric acid was present in twenty-seven instances. In other words, slightly more than two-thirds of these patients had functioning acid-producing cells in the gastric mucosa. Nine patients showed achlorhydria after histamine stimulation. Four others had anacidity after the Ewald test meal, but a histamine test was not done. It is quite possible that some of these might have produced free hydrochloric acid after histamine stimulation. Three other patients showed no free acid after the Ewald meal, but on subsequent histamine stimulation showed free acid values of 12, 13 and 28 units, respectively. Of the twenty-seven patients who did not have achlorhydria the titration value of the free hydrochloric acid was below 35 units in 16 cases. A few of the patients showed relatively high acid values. At any rate, judging from this series, we may say that atrophic gastritis is accompanied by achlorhydria in only about one-third of the cases. The typical symptoms, evidently, are not a result of achlorhydria, but a result of anatomic changes of the gastric mucosa.

#### GASTROSCOPIC FINDINGS

The upper portion of the stomach, especially the anterior wall, was the most frequent site of atrophy, but no area escaped involvement entirely. In the majority of instances the changes were patchy and varied considerably in degree. A few cases showed complete atrophy of the entire gastric mucosa. Neither the location in the stomach nor the degree of involvement could be definitely proved to have any appreciable influence on the symptomatology.\*

\*The case histories have been omitted because of lack of space.

#### ATROPHIC GASTRITIS IN PERNICIOUS ANEMIA AND COMBINED CORD DEGENERATION

(See Table II)

Since atrophic gastritis is almost always found in pernicious anemia patients, and since the patients with atrophic gastritis alone exhibited symptoms commonly found in pernicious anemia, we began a study of nine case histories of patients with pernicious anemia, in whom a satisfactory anamnesis was available. This group was comprised of seven males and two females, ranging in age from 25 to 72 years, with a somewhat higher average age than the atrophic gastritis group. In the pernicious anemia cases the digestive symptoms were less prominent and the general symptoms more prominent than in the atrophic gastritis patients. The chief digestive complaints were nausea, vomiting and belching. Only four patients complained of epigastric distress which was mild in all instances. The appetite was good in four cases, poor in four, and not mentioned in one. Of the seven cases in which a notation of the bowel habit was made, three complained of constipation. The fact that two of these patients did not complain of digestive symptoms at all (1) might have been due to the predominance of the other symptoms of pernicious anemia and an incomplete anamnesis by the examiner, or (2) it is perfectly possible that the atrophic gastritis may have been in an asymptomatic phase since these patients, as mentioned above, like those with peptic ulcer, gall stones, and many other diseases, have periodic symptoms. Friedenwald and Morrison (6) have demonstrated that no patient suffering from pernicious anemia is always free from abdominal symptoms. The general complaints were much more pronounced. All nine of these patients listed weakness and fatigue as prominent complaints. Five complained of soreness of the tongue or mouth and seven had noticed numbness and tingling or dull pains in the extremities. Gastric analysis was done in eight cases and all showed a histamine proved anacidity. Gastroscoically every patient in this group showed atrophic gastritis.

Some of these patients, even after the blood picture had returned to normal, still complained of weakness and fatigue. It seems quite possible, therefore, that these symptoms might have been due to the atrophic gastritis rather than to the insufficient amount of blood or to a deficiency state. The majority of the

TABLE II  
*Pernicious anemia*

Digestive Symptoms							General Symptoms						
Epigastric Distress													
Case	Type	Immed.	Delayed	Naus.	Vom.	Appet.	Head-ache	Vert.	Nervous-ness	Weakness Fatigue	Sore Tongue	Numbness Tingling	Free HCl
1. L.S.	fullness	x		x	x	fair	x			xxx			0
2. J.V.	distress					poor				xxxx		x	0
3. E.S.				xx	xx	good		xx		xxx		x	0
4. C.E.	pain	x	x	xx	xx			x		xx	x		
5. A.R.				xxx	xx	poor				xx	x	x	0
6. K.D.	fullness	x	x			good		x		xxxx	x		0
7. M.N.						good				xx		x	0
8. M.M.				x	x	poor		x	xxx	xx	x	x	0
9. E.O.						good				xxx		x	0

pernicious anemia patients felt well on liver extract therapy. It must be borne in mind, however, that some of the atrophic gastritis patients likewise showed symptomatic improvement with liver extract treatment and remissions without any therapy. The histories of the pernicious anemia patients showed a similarity to those with atrophic gastritis that could not be doubted. We observed one patient with atrophic gastritis and subacute combined degeneration of the spinal cord, but without blood changes suggestive of pernicious anemia. This case has been described by W. L. Palmer and R. T. Porter (14). Many of her symptoms were similar to the symptoms of uncomplicated chronic atrophic gastritis.

Thus we find that the symptoms of atrophic gastritis, pernicious anemia, and subacute combined degeneration of the spinal cord are strikingly similar in many respects.

Since we found general symptoms so frequently in atrophic gastritis, the question arose as to whether or not these complaints were common in other gastro-intestinal diseases. If such were the case, these symptoms would be of no value as a diagnostic lead in atrophic gastritis. We, therefore, decided to study the histories of patients with peptic ulcer, cholelithiasis, other types of gastritis, and psychoneurosis. These studies shall be recorded as briefly as possible.

#### SUPERFICIAL GASTRITIS PLUS ATROPHIC GASTRITIS

We were able to find nine patients who showed gastroscopically a combination of superficial gastritis and atrophic gastritis with no other demonstrable pathology. The close relationship of superficial and atrophic chronic gastritis is known. The slow transition of superficial into atrophic gastritis seems to prove that atrophic gastritis may be true inflammation or the end result of true inflammation rather than the result of a deficiency state. All of these nine patients had digestive complaints which were possibly more troublesome than those of the atrophic gastritis group, but which did not present any typical pattern. Three of these patients complained of weakness and fatigue. The observation of these three cases seems to prove that the general symptoms of chronic atrophic gastritis are due to the changes of the gastric mucosa themselves, and not to a primary deficiency state.

#### SUPERFICIAL GASTRITIS

A group of ten patients with superficial gastritis was then studied. Digestive symptoms were present in all cases and were more marked than in the atrophic group. The general symptoms were almost completely lacking in the superficial gastritis group. One patient complained of increased nervousness, but there were no complaints of weakness, fatigue, sore tongue, or any disturbance in the extremities.

#### HYPERTROPHIC GASTRITIS

In a group of twenty patients with hypertrophic gastritis there were eighteen males and two females, ranging in age from 23 to 54 years. The majority of these patients gave histories suggestive of peptic ulcer. The general symptoms were inconspicuous in this group. Only one of these twenty patients complained of weakness and fatigue. Nervousness, sore

tongue, and disturbances in the extremities were not mentioned at all.

#### GASTRO-DUODENAL ULCER AND CHOLELITHIASIS

We then examined the histories of ten patients with gastric ulcer proved by X-ray and gastroscopy and the histories of ten patients with cholelithiasis determined by roentgenography, surgery, or postmortem. The digestive symptoms in these two groups require no mention here; suffice it to say that none of these patients mentioned any of the general symptoms found so frequently in atrophic gastritis.

#### PSYCHONEUROSIS

Usually the general symptoms of atrophic gastritis are regarded as manifestations of psychoneurosis. To determine whether or not psychoneurotic patients frequently offered these complaints, we analyzed the histories of ten patients who had been diagnosed as psychoneurotics. We did not include patients with digestive complaints, because they might have had overlooked atrophic gastritis. In this group there was only one patient who complained of fatigue; his complaints showed best the difference between "organic" and psychogenic fatigue. This was a young man twenty-five years of age, who had never worked because he was afraid that it would make him worse. He was financially dependent upon his mother, but did not worry about it because he knew his mother would not "throw him out." He presented multitudinous complaints of aches and pains in various parts of his body. It seemed quite clear that in this particular case the fatigue, as well as the other symptoms, was part of a defense mechanism against the distasteful prospect of going to work. None of these patients complained of sore tongue or numbness and tingling of the extremities.

The complexity of the reciprocal effects of soul and body in somatic diseases is well known. Either the integrant personality of the patient or specific psychic events may influence the origin of symptoms due to an organic disease, or may aggravate or improve such symptoms, or may even, in relatively rare instances, aggravate or improve the anatomical features of the disease; on the other hand, symptoms caused directly by the organic disease may influence the soul and even alter apparently the personality itself. These psychosomatic aspects common to every organic disease evidently cannot be discussed extensively here. Reference is made to H. Flanders Dunbar's (4) outstanding compilatory work. However, it may be said that neither in atrophic gastritis nor in pernicious anemia were the symptoms dependent upon specific psychogenic influences, but seemed to depend almost entirely upon the somatic condition, such a behavior being quite in contrast to the obvious psychogenic influences in diseases such as diabetes and gastro-duodenal ulcer (which cannot both be considered as "psychogenic" diseases, but which are somatic diseases easily influenced by rather unspecific psychic events). Obviously, the condition of any patient is aggravated when his mental stability is disturbed.

#### COMMENT

From this study of forty-one cases of uncomplicated atrophic gastritis it appears that the digestive symp-

toms of this disease are not sufficiently characteristic to be of much diagnostic value. Only a few general statements can be made. The symptoms tend to be periodic. Anorexia and nausea are quite prominent. The distress is usually of a milder type than is generally found in other gastro-intestinal disorders.

The general symptoms follow a much more constant pattern, however, and the presence of these symptoms may be considered highly suggestive of atrophic gastritis. The frequent occurrence of marked weakness and fatigue, usually coming on in spells, and often unrelated to exertion is the outstanding finding in this disease. Increased nervousness or emotional depression are common. Fatigue is a symptom common to all destructive organic diseases such as carcinoma and tuberculosis, but it is usually absent in the benign diseases of the stomach. If the general symptoms are accompanied by soreness of the tongue and numbness and tingling of the extremities (in the absence of pernicious anemia) the presence of atrophic gastritis is extremely likely.

Achlorhydria is not a necessary concomitant of atrophic gastritis. It occurred in about one-third of the cases in this group. Furthermore, there is no definite relationship between the presence or absence of free hydrochloric acid and the symptomatology of atrophic gastritis. The symptoms apparently are due to the atrophic gastritis and not to the anacidity.

Atrophic gastritis, though sometimes secondary in diseases such as Hodgkin's lympho-granuloma, leukemia and others, rather frequently occurs as a disease in itself and is not accompanied by any demonstrable pathology elsewhere in the body. It has to be considered as a serious disease; that it is capable of causing pronounced morbidity, even to the point of incapacitation, has been shown by a review of the symptoms in this series of cases. We feel, therefore, that any patient presenting complaints of this type, particularly the very distressing general symptoms, is

deserving of gastroscopic examination to determine whether or not an atrophic gastritis is present.

The knowledge of the symptomatology of atrophic gastritis and its early diagnosis are important also from another viewpoint. The fact that atrophic gastritis forms the soil for the development of carcinoma of the stomach has been well shown by Saltzman (15), Konjetzny (9), Faber (5), Hurst (8a and 8b), Schindler and Gold (20) and others. There is almost general agreement on this point by gastroscopists throughout the world. Polyps are also more apt to develop on the soil of an atrophic gastritis. The frequency of carcinomatous degeneration of these polyps has been reported by Miller, Eliason, Wright (11) and others. It is therefore of greatest importance that patients suffering from atrophic gastritis should be watched very carefully so that any carcinomatous change can be diagnosed early. An X-ray and gastroscopic examination about every six months should be strongly advised.

### CONCLUSIONS

From a study of forty-one cases of atrophic gastritis and smaller groups of patients with pernicious anemia, psychoneurosis, peptic ulcer, cholelithiasis, and the other types of gastritis, we may draw the following conclusions:

1. The digestive symptoms of atrophic gastritis are rather indefinite; the general symptoms are more characteristic, although an accurate diagnosis is possible only by gastroscopic examination.
2. The syndrome of epigastric discomfort (such as fullness, belching, heaviness and pain) and poor appetite, distressing weakness, fatigue, "inexplicable" nervousness, sore tongue, numbness and tingling of the extremities is highly suggestive of atrophic gastritis.
3. Atrophic gastritis should be regarded as a serious disease.

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# Desiccated Hog's Stomach Extract (Ventriculin) in the Treatment of Atrophic Gastritis\*†‡

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ACCORDING to Faber (1), chronic atrophic gastritis is usually found in patients with chronic anacidity (with or without pernicious anemia), and represents the irreparable end stage of gastritis. Jones, Benedict and Hampton (2), however, have recently shown that in pernicious anemia, the changes characterizing atrophic gastritis may disappear during an induced remission. Schindler (3) and Lehman (4), as well as the authors (5), have confirmed these observations. Chevallier and Moutier (6), and Lehman (4) have reported disappearance of atrophic gastritis following administration of iron in microcytic hypochromic anemia, an observation we have also been able to confirm (5). Schindler (3) reported a return of the gastric mucosa to normal following liver therapy in a case of atrophic gastritis not associated with anemia. In view of these reports and in view of the fact that we had previously found the administration of desiccated hog's stomach extract to produce symptomatic benefit in patients with achlorhydria (7) (and presumably atrophic gastritis), we decided to study gastroscopically the effects of desiccated hog's stomach extract.

According to Schindler (3), Moutier (8) and Henning (9), the gastroscopic findings in atrophic gastritis are typical and usually easily recognized. The mucosa is thin, gray, or greenish-gray in color, and the rugae are very improminent or wholly absent. These changes may be diffuse or patchy in distribution. They are more marked in the pars media and the upper part of the stomach. Because of the thinness of the mucosa, the large vessels of the submucosa become visible. These are seen as dark blue trunks with many larger branches, which are also blue, and with finer ramifications which are red. In referring to the gastroscopic criteria of atrophic gastritis, Faber (1) states, "Although control tests by anatomical investigations are still, to some extent, lacking in such diagnosed cases of gastritis, it would seem that we must accept these observations which so accurately agree with the anatomical findings we have described."

We selected for study five cases of chronic atrophic gastritis not associated with pernicious anemia, gastric carcinoma, protein deficiency, or obvious vitamin deficiency. Two of the patients were known to have had post-histamine achlorhydria for five years.

## CASE 1 — ATROPHIC GASTRITIS, ACHYLIA GASTRICA: DISAPPEARANCE OF GASTRITIS AND RETURN OF PEPSIN FOLLOWING VENTRICULIN THERAPY; RECURRENCE OF ATROPHIC GASTRITIS FOLLOWING WITHDRAWAL OF VENTRICULIN

*Clinical History:* J. C. (33921), a white male machinist, age 68, entered the Gastric Clinic, Cincinnati General Hospital, May 28, 1931, complaining of constipation of eight years' duration. For one year prior to entry he had

### CASE 1—J. C. (33921)

#### Table of gastroscopic findings and treatment

Date	Gastroscopy	Treatment
8-29-36	<i>Atrophic Gastritis:</i> Mucosa pale, rugae improminent; branching vessels seen.	Dil. HCl min. 15 t.i.d.
11-23-36	<i>Atrophic Gastritis:</i> Mucosa pale, branching vessels seen; rugae improminent.	Ventriculin 20 gms. starting 12-5-36.
3-12-37	<i>Atrophic Gastritis Improved:</i> Rugae more prominent; mucosa less pale; branching vessels present; (occasional small hemorrhage).	Ventriculin 16 to 20 gms. daily.
8-5-37	<i>Atrophic Gastritis Further Improved:</i> Rugae more prominent; no vessels seen; scattered linear mucosal hemorrhages; mucosa less pale.	Ventriculin discontinued 8-5-37.
10-4-37	<i>Marked Atrophic Gastritis:</i> Rugae absent; mucosa pale; numerous small vessels seen.	Ventriculin 45 gms. daily started 10-5-37.
1-3-38	<i>Moderate Superficial Gastritis, No Atrophic Gastritis:</i> Rugae of normal size; no blood vessels seen; mucosa reddened; slight excess of mucus.	Ventriculin 60 gms. daily (1-4-38)
3-9-38	<i>Normal Stomach:</i> Mucosa of normal color; rugae normal; no blood vessels seen.	Ventriculin discontinued Dil. HCl min. 15 t.i.d.
3-24-39	<i>Marked Atrophic Gastritis:</i> Rugae absent; grayish mottling of mucosa; branching vessels seen.	

experienced cutting, lower abdominal pains, anorexia, and loss of weight and strength.

*Physical Examination:* Essentially negative.

*Laboratory Findings:* The gastric analysis, after histamine injection, showed achlorhydria. The blood Wassermann test was negative.

*X-ray Examination:* The upper gastro-intestinal tract and gall bladder were negative. The descending colon was "spastic."

*Course:* For five and one-half years he was treated intermittently with Ventriculin, hydrochloric acid, and laxatives. There was complete control of symptoms with the use of Ventriculin in doses of 10 to 20 grams a day and incomplete relief when he was treated with hydrochloric acid. The achylia gastrica persisted. When the

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patient was given only laxatives the symptoms (except for constipation) persisted.

On August 29, 1936, gastroscopy revealed diffuse atrophic gastritis. Achylia gastrica was present without anemia. The patient was given dilute hydrochloric acid for three months with no objective effect on the gastritis. From December 5, 1936, to August 5, 1937, 15 to 20 grams of Ventriculin were given daily, and he was symptom free. There was a return of pepsin in the gastric juice, but the achlorhydria persisted. There was some improvement of the gastritis. Ventriculin was then discontinued for two months. At the end of this time there was a return of symptoms, a loss of eleven pounds in weight, and an increase in the atrophic changes. Ventriculin was then resumed in doses of 45 grams daily. At the end of two months there was a disappearance of symptoms together with the atrophic changes though a mild superficial gastritis was present. The dose of Ventriculin was increased to 60 grams daily and continued for two more months. At the end of this period the stomach appeared entirely normal.

Ventriculin was discontinued on March 9, 1938, and the patient placed on dilute hydrochloric acid, 45 minims per day. This treatment was maintained for an entire year. There was a gradual return of symptoms and, on March 24, 1939, diffuse atrophic gastritis was present.

In all, twenty-two fractional gastric analyses were done after histamine injection. A return of pepsin was noticed soon after the institution of Ventriculin therapy, but the achlorhydria persisted.

#### COMMENT

This case confirms Faber's finding that patients with chronic anacidity have chronic gastritis. It demonstrates the disappearance of the atrophic changes with the use of large doses of Ventriculin (45 to 60 grams daily) and the return of these changes after withdrawal of this extract.

#### CASE 2—ATROPHIC GASTRITIS, ACHLORHYDRIA: DISAPPEARANCE OF GASTRITIS AND SYMPTOMS FOLLOWING VENTRICULIN THERAPY; RECURRENCE OF GASTRITIS FOLLOWING WITHDRAWAL OF VENTRICULIN

*Clinical History:* G. S. (34-14265), a white male janitor, age 78, entered the Gastric Clinic, Cincinnati General Hospital, April 12, 1937, complaining of epigastric pain. He said he had suffered with slight intermittent epigastric distress and flatulence since 1922. These symptoms became particularly troublesome in 1933. The pain was sharp, occurred about one to two hours after meals, was located to the left of the umbilicus, and at times radiated

#### CASE 2—G. S. (34-14265)

Table of gastroscopic findings and treatment

Date	Gastroscopy	Treatment
6-18-37	Atrophic Gastritis: Rugae improminent; mucosa grayish; branching vessels visible.	Ventriculin 30 gms. daily.
11-1-37	Atrophic Gastritis Improved: Mucosa grayish; rugae absent; no vessels visible.	Ventriculin 45 gms. daily.
1-14-38	Normal Stomach: Mucosa normal color; rugae of normal size; no vessels and no grayish patches seen.	Ventriculin discontinued.
5-16-38	Atrophic Gastritis (mild): Rugae of normal prominence; several small grayish areas present; no vessels seen.	Dil. HCl 10 to 30 min. t.i.d.
4-21-39	Atrophic Gastritis: Rugae decreased; branching vessels seen; mucosa grayish-pink.	

towards the midepigastrium. Since August, 1936, the pain had become more severe, lasting from three to seven hours, and had interfered with sleep. Hypodermic injections were occasionally required for relief. No apparent benefit was derived from a bland diet or soda. Constipation was present. His appetite was good. There was no vomiting. There were no tarry or acholic stools. There were no urinary symptoms. The attacks of pain were not associated with jaundice, chills or fever. He had lost ten pounds and was quite weak.

*Physical Examination:* Not remarkable.

*Laboratory Findings:* Gastric analysis revealed post-histamine achlorhydria. (Pepsin was present). The blood Wassermann test was negative. The urinalysis and stool analysis were negative. There was no anemia.

*X-ray Examinations:* The gastro-intestinal series, barium enema and gall bladder visualization were negative.

*Course:* After two months' treatment with dilute hydrochloric acid, tincture of belladonna and a bland diet, the patient lost ten pounds in weight and showed no symptomatic improvement.

On June 18, 1937, gastroscopy revealed atrophic gastritis. The rugae were improminent and the mucosa grayish. On the lesser curvature of the body of the stomach, bluish branching vessels were seen.

The patient was given 30 grams of Ventriculin daily for four months and prompt symptomatic improvement occurred. However, the achlorhydria persisted. Although the appearance of the gastric mucosa was improved, atrophic changes were still present. Ventriculin was then increased to 45 grams daily, and reexamination two and a half months later revealed a normal mucosa. Ventriculin was discontinued at this point and dilute hydrochloric acid substituted. Four months later gastroscopy revealed a return of atrophic changes in the form of grayish patches.

After eleven more months of hydrochloric acid therapy, the atrophic gastritis increased although the patient remained symptomatically improved.

#### COMMENT

This case again demonstrates the presence of atrophic gastritis in a patient with anacidity. Following Ventriculin therapy, there were no subjective complaints, and the gastric mucosa became normal. When the Ventriculin was discontinued there was recurrence of the gastritis although the symptoms did not return.

#### CASE 3—ATROPHIC GASTRITIS, HYPOCHLORHYDRIA: DISAPPEARANCE OF GASTRITIS FOLLOWING VENTRICULIN THERAPY

*Clinical History:* L. S. (43234), white male machinist, age 34, was referred to the Gastric Clinic, Cincinnati General Hospital, July 12, 1937, because of epigastric pain of two months' duration. The pain was localized, appeared about fifteen to thirty minutes after meals, and was relieved by soda at times. It was produced by cabbage, and fried and greasy foods. He complained of a great deal of belching, "sour" eructations, and flatulence. The appetite was good. There was no nausea, emesis, or tarry or clay-colored stools. There was no history of jaundice; there was no loss of weight.

*Past History:* Acute rheumatic fever in 1923; congestive heart failure in 1936. Since 1936 he had been observed in the Cardiac Clinic for rheumatic heart disease with mitral stenosis and aortic insufficiency together with auricular fibrillation.

*Physical Examination:* Negative except for cardiac findings. (There was no evidence of congestive failure).

*Laboratory Findings:* The stool and urine analyses were negative. The Kahn test was negative on the blood. Gastric analysis following histamine revealed hypochlor-



hydria and the presence of pepsin. Two biliary drainages were negative. There was no anemia.

**X-ray Examinations:** Chest was negative except for cardiac enlargement presenting a "mitral configuration." Gastro-intestinal series and gall bladder visualization were negative.

**Course:** For four months he was treated with a bland diet and alkalis. Slight relief was experienced at first, but later the pain became more pronounced, was especially severe at night, and at times radiated to the back.

**Gastroscopy,** November 12, 1937, revealed diffuse atrophic gastritis. The mucosa was pale and grayish; the rugae improminent, and bluish branching vessels were visible on the lesser curvature of the body of the stomach. The patient was given 60 grams of desiccated hog's stomach (Ventriculin) daily and a bland diet for the next four months. He improved immediately. At the end of the four-month period he was symptom-free.

**Gastroscopy,** March 7, 1938, showed the rugae to be of normal size, and the mucosa of normal (orange-red) color with a slight increase in the high lights. There were no grayish- or grayish-green patches and no visible vessels. Two small mucosal hemorrhages were observed. The findings were practically those of a normal stomach.

On April 18, 1938, word was received that the patient had died suddenly of a "heart attack" at home.

#### COMMENT

This case illustrates marked subjective improvement following Ventriculin therapy associated with disappearance of atrophic gastritis.

#### CASE 4—ATROPHIC GASTRITIS, HYPOCHLORHYDRIA: MARKED IMPROVEMENT FOLLOWING VENTRICULIN THERAPY

**Clinical History:** B. F. (41632), negress, age 21, entered the Gastric Clinic, Cincinnati General Hospital, December 4, 1936, because of severe abdominal pain of three months' duration. She said for the past ten years she had had vague abdominal pain, belching, flatulence, and constipation. The severe pain, of a stabbing character, was located in the left hypochondrium and occurred about fifteen minutes after meals. It kept her awake at night. Food or soda did not relieve it, but vomiting, which occurred frequently, did. Her diet seemed adequate in proteins and vitamins though she complained of anorexia and drank alcohol in small amounts occasionally. She had lost ten pounds. There were no chills, fever, or jaundice. Her stools had never been tarry or acholic.

**Past History:** Not significant except for a primary luetic lesion followed by a secondary eruption at the age of 14 for which she had never been treated.

**Physical Examination:** Essentially negative except for evidences of lues.

**Laboratory Findings:** Gastric analysis following histamine showed hypochlorhydria and the presence of pepsin. The urinalysis and stool analysis were negative. The blood Wassermann test was strongly positive. There was no anemia.

**X-ray Examinations:** A gastro-intestinal series and gall bladder visualization were negative.

**Course:** Atrophic gastritis was revealed by gastroscopy on December 14, 1936. Advised to take 30 grams of Ventriculin daily, she did so irregularly. Gastroscopy, June 14, 1937, revealed persistence of the atrophic gastritis. The mucosa was pale and glistening, the rugae improminent, and numerous blood vessels were seen throughout the body of the stomach.

She then took 30 grams of Ventriculin daily for almost two months with disappearance of her symptoms. Re-examination August 5, 1937, showed marked improvement in the appearance of the stomach. Although the rugae were still improminent, the color of the mucosa was

normal, and no vessels could be seen. When she returned four months later, December 20, 1937, after receiving only 500 grams of Ventriculin since her previous examination, she was still symptom-free. However, gastroscopic examination showed patchy atrophic changes.

The patient failed to return for further observation and treatment.

#### COMMENT

This case demonstrates almost complete disappearance of atrophic gastritis associated with marked subjective improvement after two months of 30 grams of Ventriculin a day. With less Ventriculin therapy, the atrophic gastritis either persisted or, having disappeared, returned.

#### CASE 5—ATROPHIC GASTRITIS, ACHLORHYDRIA: DISAPPEARANCE OF GASTRITIS FOLLOWING VENTRICULIN THERAPY; RETURN OF HYDROCHLORIC ACID ONE YEAR AFTER VENTRICULIN WAS DISCONTINUED

**Clinical History:** C. E. (84804), white male, unemployed machinist, age 62, entered the Gastric Clinic, Cincinnati General Hospital, December 1, 1931, complaining of pain in the right side of the abdomen of two months' duration. The pain was cramping in nature, radiating from the right upper quadrant to the mid-epigastric region. It occurred one-half hour to two hours after meals,

#### CASE 5—C. E. (84804)

##### Table of gastroscopic findings and treatment

Date	Gastroscopy	Treatment
4-7-36	<b>**Gastritis, Early Atrophic:</b> Upper part of lesser curvature, grayish-blue patch.	Laxatives; later dil. HCl.
11-21-36	<b>Atrophic Gastritis:</b> Rugae very improminent; numerous vessels near cardia; mucosa pale.	Ventriculin 30 grms. daily.
1-5-37	<b>Atrophic Gastritis:</b> Rugae still improminent; branching vessels near cardia; mucosa pale.	Ventriculin 30 grms. daily.
3-29-37	<b>Normal Stomach:</b> Rugae of normal size and color; no grayish patches or visible vessels.	Ventriculin discontinued.
10-15-37	<b>Normal Stomach:</b> Rugae prominent; color good; no vessels seen; no grayish patches.	No therapy.
5-16-38	<b>Superficial Gastritis:</b> Rugae normal size and color; scattered areas of hyperemia; no vessels or atrophic patches; excess of mucus present; several mucosal hemorrhages.	No therapy.
11-22-38	<b>Normal Stomach:</b> Rugae normal in size and color; no vessels seen.	No therapy.
3-21-39	<b>Normal Stomach:</b> Rugae normal in size; no vessels seen.	No therapy.

\*\*Examination made by Dr. R. Schindler.

occasionally awakened him at night, and was not relieved by food or soda. His appetite was good, but he was afraid to eat because of the pains that might follow. He had no colic, jaundice, acholic stools, nausea, or vomiting. There was no loss of strength or weight. He complained, too, of moderate constipation, belching and grumbling noises in his intestines.

**Past History:** He had a depressed skull fracture in 1918 for which he was operated upon and following which he had both petit mal and grand mal seizures. The remaining past history was negative.

**Physical Examination:** Not remarkable except for a palpable liver which was firm and extended four finger-breadths below the right costal margin but which later receded to normal.

**Laboratory Findings:** The gastric analysis showed a post-histamine achlorhydria. (Pepsin was present). The

stool and urine analyses were negative. Biliary drainage was negative. The blood Wassermann test was negative. There was no anemia.

**X-ray Examinations:** A gastro-intestinal series was negative. The gall bladder failed to visualize on two occasions.

**Course:** The patient was observed in the Gastric Clinic for five years. His symptoms were controlled by Ventriculin, in doses of 10 grams daily, or, to a lesser degree, by dilute hydrochloric acid. Post-histamine achlorhydria was present on numerous occasions.

Dr. Rudolf Schindler gastroscoped him April 7, 1936, and found an early localized atrophic gastritis.

After a little over two months of a bland diet and laxatives, he was given 30 drops of dilute hydrochloric acid daily with apparent symptomatic benefit. However, on November 21, 1936, gastroscopy revealed increase in the atrophic gastritis. He was then placed on 30 grams of Ventriculin daily and showed further subjective improvement. Evidence of atrophy was still present in the gastroscopy on January 5, 1937, but after two more months of Ventriculin therapy, no atrophic changes were found. The achlorhydria persisted. All medication was discontinued on March 29, 1937. There was no return of the atrophic gastritis and the patient continued to be symptom-free. Free hydrochloric acid appeared in the gastric contents on March 16, 1938, and on at least ten more occasions among a total of thirteen analyses done between that date and May 12, 1939.

#### COMMENT

This case illustrates disappearance of atrophic changes after four months of Ventriculin therapy

with no return of these changes after two years of no therapy. One year after the discontinuance of Ventriculin therapy there was a return of free hydrochloric acid in the gastric secretion. Whether this occurred spontaneously or as a result of the Ventriculin is not known. The gastric mucosa was normal on several examinations made during the two years after the Ventriculin was discontinued, and there was no return of symptoms during this time.

#### SUMMARY

Case histories are presented of five patients with a gastroscopic diagnosis of chronic atrophic gastritis not associated with other gastric disease, pernicious anemia, or other anemia, protein deficiency, or obvious vitamin deficiency. The patients were given hog's stomach extract, Ventriculin, in doses averaging 30 to 60 grams per day in addition to a bland or regular diet. All five patients showed marked symptomatic improvement together with disappearance of the atrophic changes. When the Ventriculin was withdrawn in three of the patients, two showed a return of the atrophic changes and one an associated return of symptoms. In a fourth patient atrophic changes reappeared when Ventriculin was taken in a total dosage of 500 grams during a period of four months.

These results suggest that atrophic gastritis in some instances may be due to a deficiency of a substance contained in desiccated hog's stomach extract.

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## "Clubbed Fingers" and Ulcerative Colitis

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IN the course of certain chronic diseases, especially those that involve the lungs, pleura or heart, an interesting deformity of the fingers may develop. This is characterized by a bulbous enlargement of the distal phalanges, associated with thickening and double curvature of the nails. The condition customarily is referred to as "clubbed fingers." The toes may be similarly affected. Enlargement of the terminal phalanges involves mainly the soft tissues, although there may be slight tufting and osteophyte formation on the bones. The change in the soft tissues consists at first of edema and a low grade of inflammation or the latter may exist alone; later, fibrosis or deposition of fat occurs. In the more severe forms of the condition, the bones of the hands and wrists may become considerably enlarged as the result of subperiosteal

proliferation of bone. The bony changes seldom extend proximal to the upper third of the humerus or femur, but in some cases the whole skeleton may be involved.

#### CLUBBED FINGERS

Clubbed fingers have been recognized since antiquity. Hippocrates observed their occurrence in certain cases of empyema. Subsequent writers have described them in association with advanced phthisis. Von Bamberger, in 1889, first called attention to the changes which might occur in the long bones. Two years later, Marie gave his classic description of the condition and bestowed on it its popular misnomer, "osteoarthritis hypertrophique pneumique" (hypertrophic pulmonary osteo-arthritis). In the early part of the present century, numerous attempts were made to dissociate simple clubbing of the fingers and hypertrophic osteo-arthritis. The exhaustive

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studies of Locke (11, 12), however, have established fairly well the identity of the two conditions.

Clubbing of the fingers is seldom a primary condition, although occasional cases do appear in which most careful search has failed to reveal any primary disease (6). In approximately 78 per cent of the cases, the condition is secondary to disease of the respiratory system (Locke) (12). Bronchiectasis, pulmonary tuberculosis, empyema, mediastinal or lung tumor, are the primary affections commonly present. The circulatory system may be the site of the primary disease, valvular and congenital defects being the common lesions. Isolated cases have been reported to follow various disorders of the kidneys and liver, amyloid disease and cachexia strumipriva and neuropathic and familial varieties of clubbed fingers have been discussed.

*Pathogenesis.* Because most of the cases of clubbed fingers have occurred in association with disease of

the respiratory system, the name coined by Marie is usually applied to the condition. This not only has resulted in the widespread use of incorrect terminology but also has influenced the direction of investigation into the pathogenesis of the condition, placing undue emphasis on mechanical factors. Experimental attempts to produce hypertrophic osteo-arthritis have consisted mainly of endeavors to embarrass pulmonary circulation by the induction of chronic cough, the introduction of foreign material into the pleural cavity or lung or the exclusion or removal of portions of the lungs (7, 8, 18). They have been uniformly unsuccessful. Circulatory stasis and anoxemia remain the most popularly accepted etiologic factors.

Von Bamberger stressed the importance of toxins in the production of periosteal proliferation. His hypothesis, although it lacks experimental confirmation, has many adherents. By way of compromise, other workers have suggested that toxins predisposed

TABLE I  
Summary of significant findings in case reported

Case	Sex, Age	Duration of Symptoms	Number of Stools Daily	Vomiting	Fever	Loss of Weight (pounds)	Hemoglobin, gm. Per 100 cc.	Roentgenologic Findings	Proctoscopic Findings	Associated Conditions	Diagnosis	Condition of Extremities	Present Status (2 Years or Less Since Admission)
1	M 30	17 mos.	15—24	+		70	11.9	Chronic ulcerative colitis from hepatic flexure to mid-sigmoid; severe involvement of terminal portion of ileum.	Rectum scarred, contracted; bleeds easily.	Perirectal abscesses; rectal fistula; rectal incontinence.	Chronic ulcerative colitis with extensive ileitis.	Osteo-arthritis of fingers.	Dead.
2	M 25	3 yrs.	7—12	0	± chills	35	7.6	Chronic ulcerative colitis involving entire colon.	Sigmoid most affected. Mucosa edematous, ulcerated, bleeds easily.		Chronic ulcerative colitis, type 3.	Early osteo-arthritis of fingers.	Improved.
3	M 21	4 yrs.	15—20		±	+	6.8	Chronic ulcerative colitis involving entire colon with marked shortening, deformity and polypoid changes; severe involvement of terminal portion of ileum.	Lumen contracted to half its normal size; polyps present; bleeds easily.	Entameba intestinis present; hay fever; osteitis of right femoral condyle.	Chronic ulcerative colitis with ileitis, type 1.	Clubbing of all fingers.	Improved.
4	F 31	2 yrs.	5—6	0		+	9.1	Chronic ulcerative colitis involving entire colon; most severe changes in right half of colon.	Lower half of rectum bleeds easily.	Amenorrhea; joint pains (knees especially).	Chronic ulcerative colitis, type 1.	Osteo-arthritis of fingers.	Dead.
5	M 55	9 mos.	15—20	0			10.8	Chronic ulcerative colitis, distal to hepatic flexure.	Mucosa granular. Bleeds easily. Contraction 1 on a basis of 1 to 4.	Bronchitis, old tuberculous lesions both apices, spina bifida occulta, relaxed anal sphincter.	Chronic ulcerative colitis, type 1.	Osteo-arthritis.	Dead (following ileostomy elsewhere).
6	M 27	10 yrs.	6—12	0		0	9.9	Chronic ulcerative colitis, midtransverse colon to rectum.	Lumen contracted to 1.2-2.0 cm. Irregular scarring. Bleeds easily.	Perirectal abscess. Rectal fistula; rectal incontinence; mastitis.	Chronic ulcerative colitis, type 1.	Marked clubbing of fingers and toes.	Improved (ileostomy).
7	F 24	2 yrs.	10	0		25	9.8	Chronic ulcerative colitis involving the colon proximal to the sigmoid; polypoid changes and severe involvement of terminal portion of ileum.	Numerous polyps present in scarred, contracted rectum.	Polyposis.	Chronic ulcerative colitis, type 3.	Marked osteo-arthritis of all fingers.	Improved.

the bones to the effects of circulatory stasis, thus inducing proliferation. Subtle changes in the calcium-phosphorous ratio, enterogenous cyanosis such as that associated with sulfhemoglobinemia or methemoglobinemia, and the stimulating effect of subperiosteal bubbles of nitrogen have been advanced as etiologic possibilities. Attempts have been made to place the blame on an arthritic diathesis, on tuberculosis and on disturbances in the function of various endocrine glands.

It is not our purpose in this paper to add to the confusion regarding etiology; rather, it is to emphasize the fact that the bowel may be the site of the primary disease and that the supradiaphragmatic organs exercise no etiologic monopoly over hypertrophic osteo-arthropathy.

#### CLUBBED FINGERS IN ASSOCIATION WITH DISEASES OF THE BOWEL

Reports of clubbed fingers in association with lesions of the bowel are few. In a review of the subject of osteo-arthropathy published last year, Penitschka stated that the cases in association with dysentery were so isolated and so inaccurately described as to make it impossible for one to decide whether the conditions were purely coincidental or actually bore a relationship to each other. This criticism certainly would apply to the case reported by Renner, in 1890, but in 1897, Teleky reported a bona fide case of osteo-arthropathy which developed in the course of severe diarrhea. More recently, several apparently authentic cases have been described in the French literature. Bensaude, Hillemand and Augier reported three cases of clubbed fingers associated with polyposis of the colon. At the same time, Brulé and Lièvre and, in 1935, Metzger, Ohlmann and Halff reported similar cases. Lemierre and Lévesque, in 1932, published the case history of a man who had clubbed fingers and toes following amebic dysentery of six years' duration. Brulé, Hillemand and Gaube, in 1937, described two more such cases, both following amebic dysentery of long standing. Two cases of clubbed fingers following inflammatory rectal strictures of two years' duration were reported, in 1932, by Moulouguet and Salomon. One of us (Bargen), in a monograph on "The Management of Colitis," in 1935, mentioned that "hypertrophic osteoarthropathy . . . is observed occasionally in cases of long standing chronic ulcerative colitis."

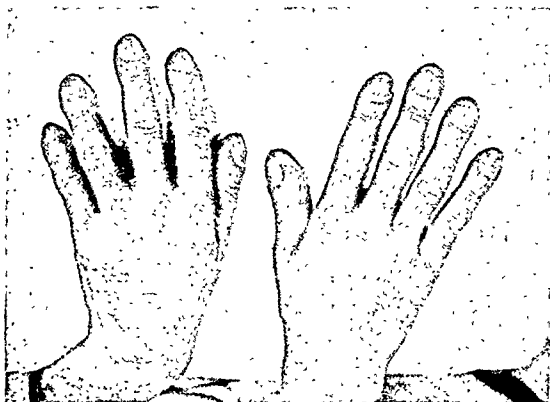


Fig. 1 (Case 6). Severe clubbing of the fingers.



Fig. 2 (Case 6). Roentgenologic changes of the digital phalanges.

In spite of the extensive investigations on chronic ulcerative colitis which have been carried out in the last twenty years, there has been no other mention of clubbed fingers as a sequel. This seems strange because clubbing of the fingers has been encountered so frequently in the comparatively severe cases of ulcerative colitis seen at The Mayo Clinic as no longer to occasion surprise. A review of seven cases of clubbed fingers occurring in patients under treatment for chronic ulcerative colitis within the past two years at The Mayo Clinic is herewith presented.

#### CLINICAL STUDY

A summary of the significant features in the records of the seven patients who had clubbed fingers in association with chronic ulcerative colitis is recorded in Table I. There were five men and two women. All but one of the patients, a man, aged fifty-five years, were in comparatively early adult life, the period in which chronic ulcerative colitis is most common. All suffered from severe disease of the bowel. The duration of the complaints in respect to the bowel ranged between nine months and ten years, with two to four years as the average. The chief symptom was severe diarrhea with blood in the stools. Three patients were aware of having had fever before admission. All had lost weight, two patients had had perirectal abscesses



Fig. 3 (Case 6). Severe clubbing of the toes.

with the resulting formation of a fistula and one of the women had amenorrhea.

On admission, all of the patients appeared poorly nourished or emaciated and anemic. In none did physical examination disclose any abnormality of the heart or lungs. One woman had slight diffuse enlargement of the thyroid gland and one man had slight, tender enlargement of both breasts. Most of the patients displayed severe abdominal tenderness when first seen. Edema of the feet and ankles was noted in two cases.

Digital and proctoscopic examination of the rectum revealed abnormalities in every case. Bleeding on slight trauma was the most common finding. Edema, granular appearance, scarring or contracture were found in varying degrees in most of the cases. Polyps were present in two of the cases. Incompetence of the rectal sphincter was found in three cases; rectal fistulas were present in two of these.

The most consistent laboratory finding was evidence of hypochromic anemia. Values for hemoglobin ranged between 6.8 gm. and 11.9 gm. per 100 cc., whereas the number of erythrocytes was proportionately higher, 3,590,000 to 4,840,000 per cubic millimeter. Leukocytes numbered between 5,000 and 10,000 per cubic millimeter, the majority being in the vicinity of the lower figure. In the absence of significant leukocytosis, myeloid activity was manifested by the high incidence of nonfilamented forms encountered in the study of stained blood smears. The flocculation test for syphilis gave negative results in every instance. Normal specimens of urine were obtained from all of the patients. *Embadoomonas intestinalis* was found in the stools of one patient; examination of the stools of

the other patients revealed nothing remarkable except the presence of blood and pus.

Roentgenologic examination of the colon after administration of a barium enema showed extensive severe chronic ulcerative colitis in all cases. Polypoid changes were demonstrable in the two cases in which such lesions had been discovered proctoscopically, with extensive involvement of the terminal portion of the ileum in three of the cases, in addition to the colonic lesions.

Roentgenologic examination of the thorax revealed no abnormality in five of the patients. Old, fibrous, inactive tuberculous lesions were present in the apices of both lungs in one case; in the other, evidence of a healed primary complex was seen.

All cases showed clubbing of the fingers. This varied from slight enlargement of the tips with "beaking" of the nails to classical "trommelschlägel" deformity with associated bony changes. In most of the cases, clubbing was of comparatively severe degree but only in Case 6 was the condition of the toes noted (Figs. 1 to 4).

Other skeletal lesions were few. One patient was found to have osteitis of the lower end of the right femur, which was thought to be of traumatic origin.



Fig. 4 (Case 6). Roentgenologic changes of the toes.

The woman who had amenorrhea complained of joint pains, especially in the knees. The fifty-five year old man had spina bifida occulta and hypertrophic arthritis of the sacro-iliac joints.

The best indication of the severity of the primary disease in these cases is the fact that, of these seven patients who had severe chronic ulcerative colitis, three are now dead, although only two years or less have elapsed since their hospitalization. Of the remaining four, one has had a colostomy performed and only two are known to be considerably improved.

### COMMENT

In none of these cases was there evidence of any primary disease, save that existing in the bowel. Since clubbing of the fingers is usually a secondary condition, it would seem that chronic debilitating, inflammatory disease of the bowel may serve as its precursor, in the same manner as affections of the lungs or pleura. To explain the occurrence of clubbed fingers as a sequel of ulcerative colitis is as unsatisfactory as

attempting to explain its occurrence in association with other conditions with which it is more commonly associated. It may only be said that it would be difficult to hold mechanical factors responsible in these cases, except in so far as debility is capable of affecting the circulation. Bacteria and their toxins, anemia with resulting relative anoxemia, faulty intestinal absorption, all, are present in severe cases of ulcerative colitis but the possible role of these factors in the production of hypertrophic digital changes remains a matter of conjecture.

### SUMMARY

In each of the seven cases of clubbed fingers presented there was associated severe chronic ulcerative colitis. Clubbing of the fingers occurs as a sequel of chronic ulcerative colitis more commonly than is generally realized. Chronic debilitating inflammatory disease of the bowel may lead, in certain cases, to digital deformity in the same manner as disease of the lungs.

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## The Effect of Barbiturates on Digestive Secretion\*

By

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A SURVEY of the rather voluminous literature on barbiturates reveals the singular fact that studies pertaining to the effect of barbiturates on digestive secretions, and the excretion of barbiturates in these juices, are almost entirely lacking. Tatum and Parsons (1), in a short note, merely state that barbital diminished gastric secretion less than ether and that after anesthetic doses of barbital, pancreatic secretion was as good as under ether anesthesia, while Barlow (2), in a report on pancreatic secretion, incidentally mentioned that he used sodium barbital as an anesthetic in acute experiments in which he was able to collect satisfactory samples of pancreatic juice.

The present study was undertaken (a) to collect data concerning the secretion of digestive juices

under the influence of various doses of barbiturates, and (b) to determine the concentration of barbiturates excreted in the gastric and pancreatic secretions.

### EXPERIMENTAL

Adult dogs were used throughout these studies. The gastric secretion was studied in animals with Heidenhain and Pavlov pouches, the pancreatic secretion in animals with permanent pancreatic fistulae of the Elman-McCaughan type, and bile secretion in the dog with a permanent biliary fistula. The surgical procedures were carried out under ether inhalation anesthesia with rigid aseptic technique. Experiments were commenced on the third to the seventh post-operative day, and the animals were fed liberally of raw meat before the intravenous injection or oral administration of barbiturates. When non-anesthetic

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doses of these compounds were employed (such as 100 milligrams of sodium barbital per kilogram)\*, the animals would usually eat following the injection. The amount of barbiturates in the digestive secretions was estimated according to the methods of Koppanyi et al (3, 4).

#### A. Effect of Barbiturates on the Secretion of Digestive Juices

1. *Gastric Secretion:* Two dogs with Heidenhain pouches and one animal with a Pavlov pouch were

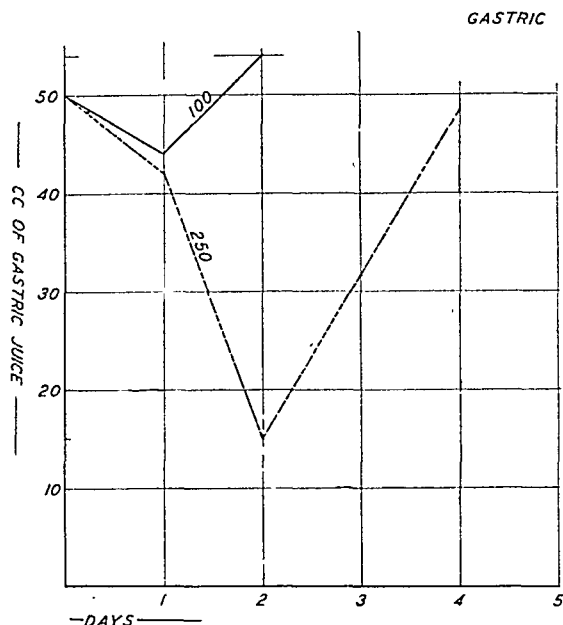


Fig. 1. Upper line 100 represents the effect of 100 milligrams sodium barbital on the volume of gastric secretion of a Heidenhain pouch dog weighing 10.9 kilograms. Lower line 250 represents the effect of 250 milligrams sodium barbital on the volume of gastric secretion of a Heidenhain pouch dog weighing 9.6 kilograms.

used in these experiments. The Heidenhain pouch animals received 100 milligrams and 250 milligrams of sodium barbital respectively by vein. The animal with a Pavlov pouch received 250 milligrams of sodium barbital and 100 milligrams of sodium amyral intravenously in two consecutive experiments one week apart. Throughout the duration of the experiment the gastric juice was collected through the fistulous stoma of the pouch in the trained or anesthetized dogs for five hours following the daily meal. Fig. 1 shows two typical experiments on the effect of a hypnotic and of an anesthetic dose of sodium barbital on the five hour postcibal gastric secretion. In every instance, with both Heidenhain and Pavlov pouch dogs, there was a decrease in the volume of gastric secretion as compared to the secretion in a previous control experiment. As shown in Fig. 1, the larger the dose of the barbiturate, the greater was the reduction of the postcibal gastric secretion, and the more delayed was the return to normal flow. In most experiments there seemed to be an increase in the se-

cretion of mucus in the gastric juice following the injection of barbiturates.

2. *Pancreatic Secretion:* Three dogs, each receiving 100 milligrams of sodium barbital intravenously, were employed for pancreatic secretion studies. In a subsequent experiment one of these animals received an oral dose of 100 milligrams of sodium amyral. A sterile rubber balloon connected with the cannula was utilized to collect the total pancreatic secretion. Fig. 2 shows the results of a typical experiment. The volume of pancreatic secretion dropped sharply under the effects of barbiturates, and in one case the flow ceased completely. The cessation of the flow was not due to obstruction or dislodgement of the cannula, as was shown by subsequent postmortem examination.

3. *Bile Secretion:* No reduction in the flow of bile was observed in one dog receiving 50 milligrams of sodium amyral intravenously.

#### B. Excretion of Barbiturates in Digestive Secretions

1. *Gastric Secretion:* Following the administration of 100 milligrams of sodium barbital intravenously to one animal, the concentration of barbital varied from 0.05 milligrams to 0.08 milligrams per cubic centimeter on the first day, decreased to 0.005 milligrams on the second day, and could not be detected in the gastric juice on the third day. Following the administration of 250 milligrams of sodium bar-

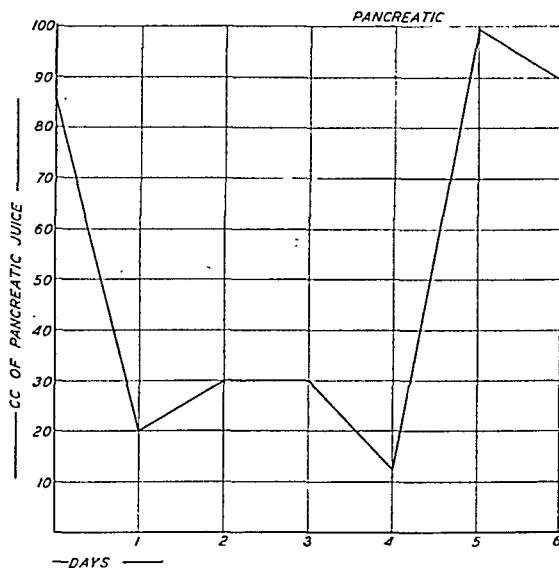


Fig. 2. Dog weighing 10.7 kilograms with permanent pancreatic fistula. The graph represents the effect of an intravenous injection of 100 milligrams of sodium barbital on the volume of pancreatic secretion for six consecutive days following administration.

bital in a representative experiment, the concentration of barbital in the gastric juice was 0.4 milligrams per cubic centimeter on the first day, 0.1 milligrams per cubic centimeter on the second day, and gradually disappeared during the next few days. In every case the dogs excreted from the pouch less than 1.0 per cent of the total dose administered. The secretion from both the Heidenhain and Pavlov pouches represented approximately one-sixth of the total gastric juice. For example, in one animal 3.6 milligrams of

\*All doses are expressed in terms of milligrams per kilogram of body weight. The latter phrase is omitted to avoid repetition.

the total dose of 1090 milligrams was excreted from the miniature stomach during the postcibal collection period in three days. In another, 20.65 milligrams of a total dose of 2400 milligrams was excreted in the gastric juice from the pouch. In an exceptional case, in the Pavlov pouch dog, in which the decrease of flow was very marked, the concentration of barbital in the gastric juice attained a level of 1.35 milligrams per cubic centimeter following the administration of 100 milligrams of sodium barbital, and 0.1 milligrams per cubic centimeter following the administration of 50 milligrams of sodium amytal intravenously. But even in this animal the output of the barbiturate in the pouch juice was only 0.9 per cent for barbital and 0.1 per cent for amytal, which represents a total gastric excretion of 5.4 per cent and 0.6 per cent respectively.

2. *Pancreatic Juice:* In some animals, following the injection of 100 milligrams of sodium barbital intravenously, no barbital was detectable in the pancreatic juice on the first day inasmuch as the secretion stopped altogether. Other animals excreted only slight amounts of barbital on the first day. In a typical experiment on the animal represented in Fig. 2, the concentration of barbital on the second day was 0.15, on the third day 0.09, on the fourth 0.06, on the fifth 0.0025, and on the sixth 0.001 milligrams per cubic centimeter. Following the administration of 100 milligrams of sodium amytal by mouth to another dog, the drug appeared in the pancreatic secretion on the first day, the concentration in the first six hours (18 cubic centimeters of juice) being 0.03 milligrams per cubic centimeter, and during the following eighteen hours (19 cubic centimeters of juice) it increased to 0.14 milligrams per cubic centimeter. Further figures could not be obtained since the flow of juice ceased in this particular animal. In no case did any dog excrete in the pancreatic juice more than 1.0 per cent of the total dose administered. One animal excreted 7 milligrams of a total dose of 1680 milligrams of sodium barbital, while another excreted 9 milligrams of a total dose of 1070 milligrams of sodium barbital and only 3.4 milligrams of a total of 1060 milligrams of sodium amytal in a subsequent study.

3. *Bile Secretion:* The amount of barbiturates in the bile was not determined due to the interference of the bile pigments in the colorimetric estimation of the drug.

It should be stated that the loss of a fraction of the barbiturates in the digestive secretions did not affect

the recovery time from the hypnosis of anesthesia produced by these drugs.

## DISCUSSION

The results obtained in these experiments indicate that hypnotic and anesthetic doses of barbiturates interfere with gastric and pancreatic secretion. They also show that only small fractions of the barbiturates administered are excreted in the pancreatic juice, while rather significant amounts of the drugs may be excreted in the gastric juice.

Since this appears to be the first systematic study on the effect of barbiturates on gastric and pancreatic secretions, and the excretion of barbiturates in these secretions, it may be well to call attention to a possible clinical significance of these findings. Barbiturates are used clinically, both in hypnotic and anesthetic doses, and in individuals having organic and functional gastro-intestinal disorders. It should be kept in mind that a significant depression of the gastric and pancreatic secretions may follow the use of barbiturates in these cases. The experimental data indicate that the return to normal flow is rather prompt after hypnotic doses, whereas after anesthetic doses the secretions may be markedly depressed for as long as four days. The hyposecretion of gastric juice following barbiturates may explain at least in part the benefit of these drugs as adjuncts in the therapy of peptic ulcer.

Although rather significant amounts of administered barbiturates are excreted in the gastric juice, it is felt that gastric lavage, unless repeated frequently, is not warranted in the treatment of poisoning from toxic amounts of these drugs given parenterally, or after complete absorption of a large oral dose. Continuous gastric siphonage in such cases may be of some therapeutic value.

## SUMMARY

Barbiturates in large hypnotic and anesthetic doses produce a reduction of the gastric and pancreatic secretions, with a prompt return to normal flow after hypnotic doses, and a delayed return after anesthetic doses. Barbiturates are excreted in the pancreatic juices in very small amounts, and the maximal postcibal excretion in the gastric juice is approximately 5 per cent.

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# The Vitamin B Complex and its Constituents in Functional Digestive Disturbances\*

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ONE of the most difficult tasks confronting an investigator in the medical sciences is the assay of a new therapeutic agent in the treatment of a functional disturbance when subjective findings alone are available. Nevertheless, if progress is to be made, such conditions must be studied by such means as are available. Positive conclusions may not be permissible, but opinions obtained as the result of study may stimulate further observations by others, and similar conclusions on the part of numerous investigators may finally achieve the status of facts. It is in this spirit that we have approached an investigation of the effect of the Vitamin B complex as a whole, and of such individual fractions as are available, on functional digestive disorders.

So-called functional gastro-intestinal disturbances perhaps constitute the majority of all digestive conditions for which the physician is consulted. While rarely threatening the life of the individual, these disturbances are only too often the cause of chronic invalidism. Treatment is but too frequently unsatisfactory, or may give adequate results only at the cost of drastic modifications in diet at which the patient rebels and which suggest to him and others that he is not a normal person. In fact, either the dietary limitations imposed by a physician or those adopted by the patient himself may tend to produce deficiencies in certain essential food substances.

The many facts, clinical and experimental, which relate the members of the Vitamin B complex to digestive function need not be reviewed here in detail. The more pertinent material will be considered below in relation to our own findings. But it was because of this known relationship and because it has been suggested that a considerable percentage of Americans may be deficient in the B vitamins (1, 2), and finally because we had available a high potency concentrate\* of the Vitamin B complex, that this study was undertaken. When we found that the Vitamin B complex was effective, we extended our observations in an attempt to determine which factor or factors were responsible for the therapeutic effect. At the time we began the preparation of this paper, the excellent contribution of Borsook, Dougherty, Gould and Kremers (3) on the same subject was published. These authors reported good therapeutic results from the administration of Vitamin B complex, and presented evidence indicating that thiamin (Vitamin B<sub>1</sub>) is not respon-

sible for the effects obtained. It is a satisfaction to be able to confirm these authors in every respect, and especially interesting since we obtained similar results with a concentrate of the extractives of yeast, while Borsook, et al, employed a rice concentrate. We are also presenting additional evidence establishing the existence of a Vitamin B deficiency in many of these patients with complaints of functional origin referable to the digestive tract. Since the existence of many factors in the Vitamin B complex has been suggested by various workers, the problem of establishing which factor or factors is responsible for the therapeutic effects is a difficult task. We believe, however, that we have also been able to obtain a partial solution of this problem.

Early in this investigation we were forced to consider whether our patients were actually deficient in any B complex factor or whether our results could be explained by a pharmacologic action of the B complex concentrate we were employing. This therapy, in many cases, was so effective that we questioned whether such a high percentage of these individuals could be as deficient as our observations indicated. We, therefore, desired some criterion of B complex deficiency in addition to the therapeutic effect of the B complex concentrate. At the time this study was undertaken, there were few methods available for the determination of deficiency relative to any member of the B complex. We finally selected the measurement of thiamin excretion in the urine by rat growth assays as open to less criticism and having a smaller element of error than any other available method. Although our assays for urinary thiamin excretion provide information concerning only one of the several factors supposed to be present in the Vitamin B complex, we believe that such determinations were the only entirely satisfactory means of demonstrating Vitamin B deficiency at the time these investigations were carried out. The fact that the various members of the Vitamin B complex are known to occur together in most foods and that multiple deficiencies of members of the B complex are common, suggests that an assay for thiamin permits us to make assumptions concerning the other components of the complex.

## METHODS

Thirty-four of our forty-four patients were dispensary cases, the rest being from private practice. Complete X-ray examinations were performed on all of our patients. No patient is included in this series in which the X-ray examination or laboratory tests suggested organic pathology, except in one case of diverticulosis of the colon where it seemed obvious

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Note: The yeast extract used is manufactured by Vico Products Co., 1919 North Clybourne, Chicago, Ill.

\*This concentrate was kindly supplied to us by Vico Products Co. Submitted July 25, 1939.

that the diverticuli could not account for all the subjective symptoms. Specifically, all patients were excluded in whom there was any question of the normality of the duodenal bulb or the function of the gall bladder. Those who had been receiving dietary management were requested to continue the same dietary practice unchanged during Vitamin B therapy. Where justice to the patient required that other forms of therapy be given concomitantly with administration

TABLE I

*Results of Vitamin B complex therapy in 44 patients*

	Number with Symptom	Satisfactory Results on Therapy	Partial Relief	No Relief	Unco-operative
Flatulence	34	22	6	4	2
Abdominal distress	31	20	5	3	3
Alternate constipation and diarrhea	21	16	2	2	1
Constipation only	13	9	1	2	1
Diarrhea only	7	4	2	1	
Skeletal pains	14	8	3	2	1
Weakness and fatigue	12	8	1	2	1
Nervousness	8	5	2		1
Anorexia	7	7			

of the B complex we have excluded the patient from our series, including only patients to whom no other treatment was administered while the effect of the B complex concentrate was being studied.

The Vitamin B concentrate that we used is made from brewer's yeast by extraction and concentration of the extract at low temperature. It contains all the water and alcohol soluble extractives of the yeast. The solid content is approximately 40 per cent, the thiamin (Vitamin B<sub>1</sub>) content 125 International Units per gram, and the riboflavin (Vitamin G) content 35 Sherman-Bourquin units per gram. At the beginning of therapy each patient received two teaspoonsful (8 grams) of this concentrate per day; after the therapeutic effect had been established the dose was frequently reduced in order to determine the minimal amount that was effective. This concentrate was given to 44 patients for periods of from 3 months to 1 year. In 11 cases the concentrate was alternated with crystalline thiamin (1500-2000 I. U. per day) and in 9 cases with riboflavin (Vitamin G) concentrate that contained no other members of the Vitamin B complex (600 Sherman-Bourquin units per day). The thiamin and riboflavin were given for comparison with whole Vitamin B complex in an attempt to determine whether these substances were responsible for any or all of the observed improvement. Since thiamin and riboflavin were found therapeutically ineffective, they constitute a control group. It may be noted that these 20 patients all showed improvement on whole complex.

Nicotinic acid was given in doses ranging from 100 to 200 mgm. per day, 100 mgm. b.i.d., p.c., being given if it did not produce a marked flushing of the skin, and a smaller dose if unpleasant reactions were ob-

tained. In no instance did 50 mgm. b.i.d., p.c., produce more than a slight feeling of warmth. A total of 42 patients received nicotinic acid, 22 of these were individuals who had previously been given, or were later given, whole Vitamin B complex.

The urinary thiamin output of 21 patients was assayed by the method of Helmer (4). Urinary thiamin excretion was also determined by the same method in individual 5 day urines from 6 normal medical students and in a pooled specimen representing the urinary excretion of 10 normal medical students for 5 days. An attempt was made to select the most typical patients for assay. Urine was collected under toluol for a five day period, each day's sample being brought to the laboratory as soon as collection was complete. The urine was adjusted to pH 4.5, and the thiamin adsorbed on 5 grams of Lloyd's reagent. The adsorbate was filtered, air dried and fed to young albino rats, previously depleted of thiamin by a thiamin-free diet.

Weighed portions of the adsorbate were mixed with small amounts of the thiamin deficient diet and fed in supplement dishes. It was found that 5 grams represented the practical limit of the amount of adsorbate which a rat would eat in 24 hours. As a result, 5 I. U. excretion per day was the least amount that could be assayed. Patients whose urinary output of thiamin fell below this are simply reported as less than 5 I. U. per day. Our observations confirm the general finding that after a day or two, the rats on assay readily eat an adequate supplement, but tend to spill a supplement which is nearly devoid of thiamin. The weight changes of the assay rats were compared in the usual way with gains of groups of rats which were fed international standard at two levels. A number of animals were fed yeast concentrate or crystalline thiamin to make sure that (1) the diet was deficient only in this component,

TABLE II

*Comparison of satisfactory results on Vitamin B complex and nicotinic acid*

	Percentage Satisfactory on Vitamin B Complex	Percentage Satisfactory on Nicotinic Acid
Flatulence	67	57
Abdominal distress	64	56
Alternating constipation and diarrhea	74	69
Constipation only	75	71
Diarrhea only	50	50
Weakness and fatigue	60	17
Nervousness	63	16
Anorexia	100	30

and (2) the animals were capable of normal response to the vitamin.

## RESULTS

The specific symptoms exhibited by our patients and the responses of each symptom to treatment with Vitamin B complex are listed in Table I. Similar data for a comparison of satisfactory results from the use of whole complex and nicotinic acid is shown in Table II. While the changes as listed, often occurred with

TABLE III

*Urinary output of Thiamin in patients with functional digestive disturbances and in normal individuals*

Patient	Thiamin Output (I.U. Per Day)	Clinical Result From B Complex Therapy	Chief Symptoms Prior to Therapy
1	8	Good	Distress, constipation, flatulence, starch intolerance.
2	15	Poor	Constipation, bloating (diverticulosis of colon).
3	<5	Did not return to clinic	Flatulence, constipation.
4	<5	Good	Flatulence, alternating diarrhea and constipation.
5	7	Good	Flatulence, distress, fatigue.
6	<5	Did not return to clinic	Distress, bloating, nervousness.
7	<5	Fair	Bloating, moderate distress.
8	<5	Good	Distress, bloating, alternating constipation and diarrhea.
9	9	Good	Flatulence, anorexia.
10	<5	Good	Distress.
11	18	Good	Alternating diarrhea and constipation, flatulence.
12	<5	Good	Flatulence, constipation.
13	<5	Good	Distress, flatulence, skeletal pains.
14	<5	Left city	Distress, constipation.
15	25	Poor	Constipation of long standing. Moderate distress.
16	<5	Good	Diarrhea, flatulence, distress, weakness.
17	<5	Could not tolerate complex	
18	<5	Fair	Sensitivity to specific foods alternating constipation and diarrhea.
19	<5	Fair	Alternating constipation and diarrhea, distress.
20	<5	Good	Distress, flatulence, constipation.
21	<5	Good	Flatulence only.
NORMALS			
1			20
2			45
3			<5
4			10
5			15
6			12
7-16			20
(Pooled spec.)			

surprising promptness, it is our observation that the full effect of treatment is not manifested for a considerably longer time.

Although our series of patients receiving crystalline thiamin and riboflavin concentrate is small, we wish to mention them because we believe them to be well controlled. Some had shown excellent improvement on the whole complex and were changed to either thiamin or riboflavin with recurrence of their symptoms. Others were given these substances for a considerable period of time as their first medication and subsequently responded to whole B complex. In no instance was any definite effect on gastro-intestinal tract symptoms noted as a result of thiamin or riboflavin. Results

with these materials were in striking contrast to those with whole complex or nicotinic acid.

The results of our determinations on urinary thiamin output are listed in Table III. Various authors are in agreement in giving 15 to 20 I. U. per day as the urinary excretion of normal individuals on an adequate diet. Harris, Leong and Ungley (5) conclude from their studies that an excretion of less than 12 I. U. daily indicates that the diet contains a subnormal amount of Vitamin B<sub>1</sub>. Goudsmit and Westenbrink (6) have obtained similar results by a different method. Even though we do not believe that thiamin can play an appreciable role in the therapeutic effects obtained with the concentrate that we have used, the fact that the urinary thiamin output is low in the majority of these cases strongly suggests that the diet has not been adequate in those foods that contain the B complex. Whatever fraction or fractions of the complex are responsible for the therapeutic effect may therefore be suspected of being deficient. Nicotinic acid is certainly one of these fractions but the methods for the determination of this substance are unsatisfactory, and thus far we have been unable to determine the presence of deficiency except by therapeutic test.

The rationale of the use of the B complex in functional gastro-intestinal conditions has been suggested by a large number of previous clinical and experimental studies, of which but a few can be mentioned. Borsook et al (3) have reviewed the pertinent literature and have discussed the possibility, denied by some investigators, that a condition as frequently seen as dysfunction of the gastro-intestinal tract can be due to a subclinical insufficiency of the B vitamins. Steinberg (7) reporting on the use of the B complex states that it restores normal tone whether the bowel was originally hypo- or hypertonic. Other investigators, as a rule, have related Vitamin B deficiency to atony of the bowel rather than to hypertonicity (9). The occurrence of anorexia in Vitamin B deficiency is too well known to require comment; it occurs in man and in all animals that have been studied. Constipation also, in man at least, has frequently been found to relate to B deficiency. We have not, however, been impressed by the frequency with which anorexia and constipation have occurred in our series of cases, even though these are the principal gastro-intestinal symptoms which others have correlated with lack of Vitamin B.

It was our observation that the patient who had a tendency to periods of alternating constipation and loose stools associated with abdominal distress and with flatulence was benefited most strikingly. We are well aware of the psycho-neurotic tendencies exhibited by a large percentage of these patients and also their tendency to show temporary improvement on any type of therapy offered them whether medicinal or psychic. The whole vitamin complex which we employed had a most disagreeable taste which had to be disguised for many patients. We often had the experience of patients obtaining a satisfactory result and returning 6 to 12 months later with a recurrence of identical symptoms and asking for more of the "bad tasting medicine."

Our evidence that neither thiamin nor riboflavin is the effective fraction of the Vitamin B complex may explain our observation that large dosages are neces-

sary for optimum results. The nicotinic acid content of the concentrate is not definitely known, but it is probable that the amount used supplies not more than 100 mgm. (in the form of nicotinamide) per day. Thus one of the limiting factors is presumably nicotinic acid; it is quite possible that other fractions which contribute to the therapeutic effectiveness of the concentrate are also present in small amounts relative to thiamin and riboflavin.

In a previous preliminary report by Crandall, Chesley, Hansen and Dunbar (10), evidence has been presented that the P-P factor (nicotinic acid or physiologically equivalent derivatives) is essential to normal gastro-intestinal motility. The disturbances incident to frank pellagra are well known. It therefore seems quite possible that a part of the beneficial effect of whole Vitamin B complex may be explained by restoration of normal gastro-intestinal motility in patients with a borderline P-P factor deficiency. It is unlikely, however, that this is a complete explanation of the effect of whole complex, especially since our data indicate a superiority of whole complex over nicotinic acid alone. This superiority is especially striking with regard to the effect on nervousness, weakness, and anorexia, the first two of which are often such prominent symptoms that some of the patients might be termed neurasthenic. Perhaps other fractions of the complex which are not as yet available in pure form may be essential for the full effect. Combinations of nicotinic acid, thiamin and riboflavin should also be tested at a future date to determine whether these substances in conjunction can replace the whole complex.

We do not wish to suggest that nicotinic acid in pure crystalline form should find a place in the treatment of functional digestive disorders. The use of whole Vitamin B complex appeals to us as a more rational procedure because: (1) in our experience it produces better therapeutic results, and (2) it is probable that deficiencies of several B complex

fractions are more common than deficiencies of a single factor.

The tabulation and evaluation of subjective symptoms referable to the digestive tract is difficult and is certain to be associated with an element of error. Granting this, we are of the belief that Vitamin B complex therapy offers more to many patients with functional gastro-intestinal disturbances than any of the regimes of careful dieting, antispasmodics, sedation, etc., now in common use. That the employment of the B complex is logical seems clearly indicated by our finding of a decreased urinary output of thiamin in a high percentage of our patients, which also presumes a deficiency in the other fractions of the B complex.

### CONCLUSIONS

1. A high percentage of patients with functional digestive disturbances are improved by the administration of a Vitamin B complex concentrate in large doses.
2. That these patients are deficient in the Vitamin B complex is suggested not only by the results of therapy, but also by the demonstration of an abnormally low excretion of one of the B complex constituents (thiamin).
3. Preliminary tests indicate that effectiveness of the whole complex is not due to Vitamin B<sub>1</sub> (thiamin) or to Vitamin B<sub>2</sub> (riboflavin).
4. Part of the effectiveness is due to the action of the nicotinic acid; however, the therapeutic use of pure nicotinic acid is not suggested for reasons given.

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## Peptic Ulcer Treated by Posterior Pituitary Preparations Clinical and Experimental Observations

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**T**HE disease of peptic or gastro-duodenal ulcer exhibits a number of characteristics which are intimately related to the endocrine pattern and the

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autonomic nervous system. Our efforts described in this paper have had to do mainly with these basic or endogenous mechanisms rather than with the more obvious problems concerning this syndrome.

We believe that the posterior lobe of the pituitary gland fills a most important part in regard to this disease and others before us have been of somewhat the same opinion. Rogers (1), as early as 1916, demonstrated that posterior pituitary extract would reduce

gastric secretion and he believed that it operated by way of the vegetative nervous system. These results were still later confirmed by the work of Hess and Gundlach (2) and Hoffman (3) with both human and animal experiments. This pharmacologic action was employed by Drouet (4) in 1933, along with a bland diet, in the management of peptic ulcer. The good results reported by him were confirmed by Kucikowna and Olszewski (5) and Negri (6). The reduction of gastric secretion was not a uniform finding in their hands and little mention was made of the disagreeable side actions of pituitrin given hypodermically.

The reason for our interest in this problem was the observation in a few instances of an unexplained polyuria with nocturia associated with duodenal ulcer; this was pointed out in our preliminary report (7), January, 1937, and repeated in later publications (8, 9). None of the usual causes including the taking of excess milk and alkali could explain this mild but definite disturbances of water metabolism. This original observation suggested a probable related etiology of peptic ulcer and diabetes insipidus. Beltrametti and Rettanni (10) have observed a greater response of gastric secretion to the same stimulus in cases of diabetes insipidus as compared with normal subjects. A few of our patients noticed nocturia along with loss of weight and fatigue beginning several days before the first ulcer symptoms. The total day and night urine volumes and their respective average specific gravities were followed at frequent intervals for a period of weeks in a patient who had recovered from a duodenal ulcer treated with posterior pituitary powder intranasally (Fig. 1). There was a definite upturn in both the day and night urine volumes and a diminution in the specific gravities several days before the initial symptoms of a recurring ulcer. This urinary disturbance was observed in twenty of our series of seventy-six peptic ulcer cases. Under treatment with pituitary preparations, twelve of these, all young individuals, enjoyed rapid and complete relief of these symptoms. The remaining eight cases obtained varying degrees of improvement. These symptoms might have been due in part to excessive parasympathetic tonus, which is the ejection innervation of the bladder.

Doubtless the endocrine system has much to do with the development of a certain constitutional type and gastro-duodenal ulcer is frequently found in individuals exhibiting the same characteristics (11). Sixty-nine of our patients were of a normal or linear type of body build with the great majority being of the latter sort, only seven being broad, stout individuals. Only three of these seventy-six patients were females and each had passed menopause. The family history was positive for this condition in eighteen per cent of this series, and one couple of identical male twins were treated. A nervous, intense personality was apparent in fifty instances. The blood pressure was normal, or below in every patient.

Four cases of duodenal ulcer treated by frequent hypodermic injections of pituitrin derived good results, but the disagreeable side effects prevented further use of this method of administration. Smith (12) has shown that one hundred and sixty milligrams of posterior pituitary lobe powder taken by intranasal insufflation, which is the equivalent of forty international units of pituitrin hypodermically, will control the average severe case of diabetes insipidus. This route of administration was next employed.

After instruction, the ulcer patient gave to himself forty milligrams, or approximately two-thirds of a grain of the powder, a little at a time, onto the upper absorptive nasal mucous membranes. Believing that this hormone's activity was mainly needed as the stomach empties, it was taken four times daily, about thirty minutes after each meal and at bedtime. The tip of the insufflator was inserted about one-half inch pointing backward and up into the nostril, and the patient taught to exercise exactness in blowing the powder on absorptive surfaces and allowing it to remain there, if possible, about two hours. Only very few disagreeable side actions of consequence were observed in any of the cases thus treated. Sensitivity reactions to this protein were rare with only two cases showing localized erythema of brief duration and two with headaches during the first few days of its use. A serious nasal discharge following each dose in four instances caused this method to be abandoned and the oral route substituted. Of coincidental interest are the few cases, only two, of hay fever or other nasal allergies observed in this series of ulcers.

We definitely prefer this method and have employed it in treating fifty-two patients with peptic ulceration. It should be continued in full dosage for five to six weeks and in half dosage for one or two more weeks. Satisfactory results have been obtained in varying periods of from three to nine weeks. It is advised that this powder be again taken with the first symptoms of a recurring ulcer, and it has been given in a few instances prophylactically to those individuals who have had regular attacks with each spring and fall season. We are not aware of any contraindication to the use of posterior pituitary powder by this method in the management of the ulcer syndrome, unless it be pregnancy.

Two-thirds grain of post-pituitary powder in a capsule or compressed tablet four times daily before meals was given to twenty individuals having this disease. Little or no relief of symptoms was experienced in seven cases after at least one week's trial; but each obtained the desired result when changed to the intranasal method. All patients except a few complicated ones, remained ambulatory and continued their occupation. No other medication was employed and a regular diet was taken three times daily, omitting only the most indigestible foods. Undoubtedly frequent feedings and the use of alkalies would have been helpful, with the posterior pituitary preparation employed as an adjunct, but they would have clouded our impressions and results.

This unselected group of cases, accumulating over a three year period, consists of seventy-six individuals whose ages varied widely with the average being thirty-seven years. Most patients had experienced several previous attacks before the one treated in this way. Nevertheless fifteen were observed at probably their first ulceration. This therapy was initiated in cases having had continuous symptoms from one week to one and a half years with the average being five and a half months. A previous perforation or hemorrhage was prominent in the history of several and posterior pituitary therapy was begun immediately after hematemesis in five individuals. All but two unquestionable cases had a definite peptic ulcer as diagnosed by careful fluoroscopic and film examination, and at times supplemented by gastroscopy, before

any treatment was started. The ulcer was of the duodenal bulb in every instance but four—three of these being of the gastric lesser curvature, and one of the jejunum following gastro-enterostomy. Besides frequent personal interviews, the roentgenologic examination was repeated in almost every instance, four to six weeks following the onset of treatment and thereafter at six month intervals. The disappearance of the ulcer was followed very closely by repeated X-ray studies in fifteen patients.

The excellent results obtained in these cases were striking, because of the early onset of improvement and its steady continuation in the large majority. The first relief of symptoms was experienced in as short a

time as one day, and as long as ten days from the start of treatment. As a rule no symptoms or epigastric tenderness were present after seven to twenty-one days. Aside from the specific relief, a gain in appetite, weight and strength and improved bowel function occurred frequently. It was repeatedly observed that patients slept better and were less nervous shortly after commencing the hormone.

Nine cases (one gastric ulcer) must be counted as failures although three of these having extensive duodenal deformity derived some benefit. The remaining sixty-seven cases have been divided into two groups, depending upon the findings of roentgen examination. Group I is composed of those patients having little or

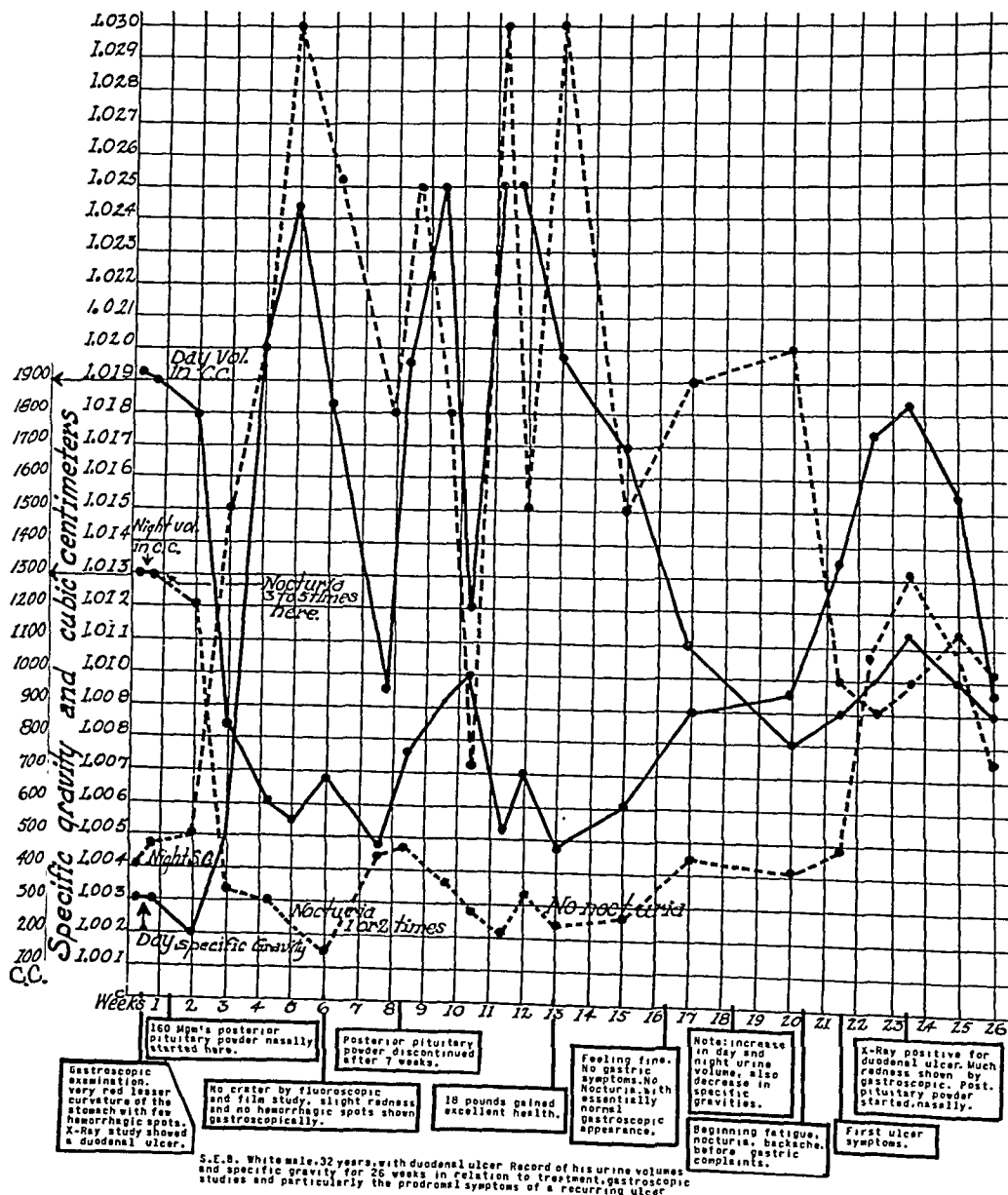


Fig. 1

no demonstrable scar accompanying the ulcer, while Group II includes those having moderate to very extensive scarring. A follow-up of three months to three years obtains for this number of cases, the average being fifteen and one-half months, and many have enjoyed continuous good health with no suggestion of recurring symptoms. The duodenal deformity has been observed either to disappear or to improve in a moderate number, but when present to function in a non-spastic, deliberate manner. Of the thirty-four patients in Group I, three experienced a recurrence in one year, and three others in over one year—a total recurrence of eighteen per cent in three years. Thirty-three cases make up Group II which had eight recurrences in one year and six more after one year—a total of forty-two per cent in three years. Two cases of this group experienced three different attacks apiece. Most encouraging is the fact that all patients having recurrences insisted upon again using posterior pituitary powder and all but two obtained satisfactory results.

Nineteen patients having hypersecretion and hypermotility without demonstrable cause have been treated with this hormone. Fifteen derived significant relief lasting several months. A few cases with functional abdominal complaints unlike those of an ulcer were given this drug with absolutely no relief. Placebos, both intranasally and orally have been administered to a few ulcer patients without either the usual subjective or fluoroscopic improvement as noted with posterior pituitary preparations.

If the disease of gastro-duodenal ulcer was accurately classified as to the predominant etiologic factor and posterior pituitary preparations were used where best suited, we believe the results would be even more impressive. Nevertheless we know that this hormone initiates and maintains a condition in the stomach and duodenum most conducive to the healing of ulcers. Several complicated cases have been healed by this procedure, but the response is of course less definite where there is a strong diathesis with much scar formation. Some patients appear to have had a lessening of their ulcer diathesis following this therapy as evidenced by a maintenance of increased weight, and much less systemic and gastric irritability to the same environmental stresses.

#### EXPERIMENTAL OBSERVATIONS AND COMMENT

The means by which pituitary preparations effect beneficial results in the ulcer syndrome affords a difficult problem. Dodds and Noble (13) have demonstrated in cats that gastric secretion in response to all types of stimulation is inhibited by injections of pituitrin. A diminution in volume and not in acidity of the secretion was the principle effect. We (7) have shown that moderately large amounts of pituitrin will in dogs prevent altogether gastric secretory response to stimulation by histamine in the usual dosage. Cutting, et al (14) state that in cats hypophysectomy abolishes the regular relationship between blood flow and secretion and consequently, the regular smooth relationship between acid and volume of gastric juice disappears. Manning, Hall and Banting (15) were able by continuous electrical stimulation of the vagus nerve in the unanesthetized dog to induce gastro-intestinal hyperemia and by combining this procedure with eserine administration to cause the formation of

ulcers. Acetylcholine is well known to increase the motor activity of the stomach and Necheles (16) reports that in small amounts it increases gastric secretion and diminishes blood flow through the stomach. He further suggests that disturbance in the balance between acetylcholine and acetylcholine-esterase is possibly a mechanism of peptic ulcer production. More recently Necheles and Neuwelt (17) have demonstrated that pituitrin in small doses prevents the usual fall in blood pressure in response to acetylcholine injections. We have confirmed this observation in experiments on a series of twenty-two dogs.

The idea that the occurrence of peptic ulcer might be the result of an imbalance in the acetylcholine-acetylcholine-esterase mechanism in which acetylcholine activity is excessive and that this imbalance is due, at least in part, to disturbed posterior pituitary function has much circumstantial evidence in its support. Lackey and Slaughter (18) have reported a moderately lowered (lowering of 23%) serum acetylcholine-esterase content in a series of peptic ulcer patients as compared with normal values established for this vicinity. They have also noted that normal values in this region are considerably higher than those reported from the northern United States and Canada. This regional difference might possibly be related to the less frequent occurrence of peptic ulcers in the South. We are not convinced, however, that serum esterase activity is necessarily a true index of the readiness with which acetylcholine is destroyed in the tissues. It appears that there is probably always an excess of esterase. We have not been able to alter the acetylcholine esterase activity of the blood serum by administration of posterior pituitary preparations to peptic ulcer patients or to dogs; nor have we found the values changed in dogs by removal of the posterior pituitary lobe.

We have studied gastric secretory response to histamine stimulation in four dogs before and after removal of the posterior pituitary body. The stomachs of the animals were evacuated by intubation and 0.02 mgm. of histamine per kgm. body weight given subcutaneously. The stomach was emptied three times at 20 minute intervals. Twenty tests were made before and fifteen after removal of the posterior pituitary lobe. In Fig. 2 are shown composite volume and composite free hydrochloric acid curves of each of the two groups of tests. It is seen that there is a definite increase in both volume and free acid after removal of the posterior pituitary lobe.

Previously we have reported (9) changes in gastric motility in ulcer patients under pituitary therapy in which there is a lessening of tone, spasm and motility of the stomach and duodenum. In forty-five fluoroscopic examinations of ten dogs whose posterior pituitary bodies had been removed, we have repeatedly observed a heightened motility and spasticity as compared with that seen in control animals. There was no constant difference in emptying time of the stomach but in the operated animals the barium meal passed into the duodenum in an erratic and irregular fashion, only segments of the duodenum being filled at any one time and the portions received from the stomach being propelled along at a great rate.

We have made gastroscopic studies on a series of seven duodenal ulcer patients during treatment with pituitary powder. Five of them were examined before

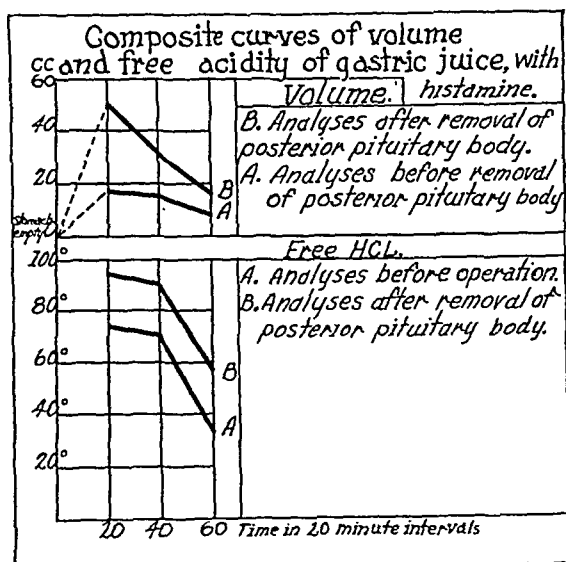


Fig. 2

initiating treatment. In every case the gastric mucosa exhibited the "ulcer stomach" hyperemia as described by Schindler (19) and in three there were mucosal hemorrhages. All were examined after three to six weeks of treatment and all except one presented an essentially normal mucosal appearance. The one exception had a partial obstruction and is one of the failures recorded in our series. Three of the group were reexamined after periods of several months when recurrences were had and the hyperemia was again present. One reexamined two months after treatment when symptom-free presented a normal mucosal picture.

A similar series of gastroscopic studies was made on a large group of normal dogs. The posterior pituitary lobe was removed from each of five of the group and further observations were made at intervals for two or three months. In order to rule out the personal element in so far as possible, all examinations were made by one of us. Normal dogs were included in each period of examination, the examiner not being told which were normal and which were operated animals until after completing his observation. An increase of redness of gastric mucosa was apparent in each case within a period of two weeks or longer. The change was much more pronounced in some animals than in others. One exhibited mucosal hemorrhage after sixty days. Two showing most pronounced hyperemia were

treated with ten units of pituitrin daily by subcutaneous injection in divided doses. Observations revealed a return to normal appearance after several weeks.

Whatever may be the immediate cause for the mucosal hyperemia in peptic ulcer patients, it seems to us very significant that a similar hyperemia may be reproduced in the dog by posterior pituitary deficiency and that in either instance its disappearance can be brought about by administration of posterior pituitary preparations. These observations are not opposed to the oft-repeated idea that peptic ulcers result from ischemia. It is obvious that venous and capillary dilatation might give a hyperemic appearance when, due to arteriolar constriction, the actual blood flow is diminished. Actually this is exactly what we should expect in a posterior lobe deficiency in that according to Krogh (20) the contractile elements of the capillaries are far more sensitive to pituitrin than is arterial muscle. Pituitrin in large doses intravenously has been shown to diminish gastric blood flow, probably by direct action on the musculature of blood vessel walls. However, we maintain that posterior pituitary principle absorbed slowly (intranasal insufflation) in small amounts increases gastric and duodenal blood flow by its antagonism to acetylcholine (vagotonia), an agent known to diminish blood flow there. This has been repeatedly demonstrated in the dog by administering an amount of pituitrin too small to raise the blood pressure but effective in completely blocking the blood pressure response to injections of acetylcholine, which would otherwise cause a profound drop. Also the dosage of posterior pituitary powder both nasally and orally employed by us has been found to raise the systemic blood pressure temporarily in only two patients.

### SUMMARY

Satisfactory clinical results are reported in sixty-seven of seventy-six cases of peptic ulcer treated with posterior pituitary preparations.

Intranasal insufflation of posterior pituitary powder has proved to be the most satisfactory mode of administration.

Neither a strict dietary regime nor other medication has been employed and the patients have remained ambulatory for the purpose of evaluating this therapy. Posterior pituitary preparations should be considered complementary to the accepted principles of peptic ulcer management.

The theoretical basis for the use of pituitrin in treatment of gastro-duodenal ulcers is discussed and experiments related thereto are described.

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## Clinical Results from the Continuous Intra-Gastric Drip Using Colloidal Aluminum Hydroxide in the Treatment of Peptic Ulcer\*

By

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AT the Jefferson Hospital for the past several years we have been using various preparations of aluminum in the treatment of ulcer patients. For the past eighteen months we have been using a continuous intra-gastric drip similar to the one devised by Woldman, in those peptic ulcer patients presenting the most severe symptoms. Practically all of the patients treated in this manner by us have shown some complicating factor which has made them resistant to the usual medical management. The purpose of this paper is to report on the method of treatment used by us, the immediate results obtained in a series of difficult peptic ulcer patients and a follow-up of these results of from six months to eighteen months. An attempt has been made to evaluate this treatment and to ascertain its place in ulcer therapy.

### DESCRIPTION OF CASES TREATED AND METHOD USED

We have treated forty cases of peptic ulcer with the continuous intra-gastric drip of colloidal aluminum hydroxide gel. Our treatment has been divided into two phases. The first phase has consisted of from seven days to fourteen days of the continuous drip treatment day and night together with dietary and other medical regulations. The second phase has been a follow-up of ambulatory treatment with the colloidal aluminum hydroxide gel given orally several times daily together with dietary restrictions and other medication still in force for a certain length of time, until clinical and roentgen evidence of definite healing had taken place. Then the follow-up continued with the patient on little or no treatment for as long as eighteen months in several cases.

The apparatus as described in Fig. 1 was used by us and is more simplified than that devised by Woldman. The patient's cooperation in keeping the solution flowing and preventing it from settling to the bottom of the container was helpful and obviated unnecessary nursing care. Sometimes we have found it necessary to increase the size of the intra-nasal Levin tube in order to facilitate the flow of the solution. A few drops of nasal oil several times daily allays any tendency toward nasal irritation. The tubes were tolerated well

and the patients had no difficulty eating soft diets with the tubes in place.

We have used colloidal aluminum hydroxide gel mixed with water, three parts of water to one part of gel, and permitted it to drip through the tube at a rate averaging fifteen to twenty drops per minute continuously day and night. The patients had bathroom privileges but were otherwise confined to bed. Eighteen of the patients had the continuous drip for seven days, eleven for ten days and ten for fourteen days.

In addition to the continuous drip, except in the cases of actively bleeding ulcers for the first twenty-four to forty-eight hours, we have permitted the patient a soft diet of three to five small feedings per day. The diet has consisted of milk, soft cooked eggs, cooked cereals, strained vegetables, gelatine products and creamed soups. If the patients felt distended or uncomfortable due to too much fluid and food, we have reduced the feedings to three a day. They have also received belladonna and small doses of phenobarbital. Tobacco and stimulants were interdicted. Thirty-one of these patients had been on previous ulcer therapy, consisting of dietary and alkaline medication with unsatisfactory results. In no case were the symptoms controlled. The only change in the treatment was the use of the drip instead of the alkaline medication. Therefore we had only this addition to the therapy and were able to make comparison as to the results from the change in therapy.

This drip was given continuously to the group of patients for periods varying from seven to fourteen days, then was removed, the patient had roentgenograms taken and then started on ambulatory treatment. During the ambulatory phase other roentgen studies were made from time to time to check on changes in the ulcer area.

Our group of forty peptic ulcer patients consisted of thirty-eight men and two women whose ages ranged from twenty-four years to fifty-five years. There were twenty-eight duodenal and eight gastric ulcers. Five of the duodenal ulcer patients and one of the gastric ulcer patients were actively bleeding when the treatment was started. In addition there were four jejunal ulcer patients following previous operations. Symptoms in this series varied from a few months to chronic digestive disturbances extending over years. Each of these patients had a definitely

\*From the Departments of Medicine and Therapeutics, Jefferson Medical College, Philadelphia. The preparation of colloidal aluminum hydroxide gel used in this study is Amphojel prepared by John Wyeth and Brother, Philadelphia. Their assistance in this study is appreciated.

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proven ulcer both by clinical and roentgen findings with the exception that four of the bleeding cases had no roentgen examination until after the bleeding had ceased. The other bleeding patients had previous roentgen studies before they presented signs of hemorrhage.

In each patient, except those actively bleeding, a gastric analysis was made before treatment was instituted. All patients were weighed, and complete blood counts, urinalyses and careful physical examinations. Records were kept as to symptoms, weight, intake and output of fluids and samples of gastric secretion were taken during the treatment from time to time. In the case of the bleeding ulcers nothing was given by mouth except the continuous aluminum hydroxide gel drip for the first twenty-four to forty-eight hours, then the same feeding procedure as in the other ulcer cases was started, except in smaller amounts. Fluids

within twelve hours, eight within twenty-four hours and the remaining four within thirty-six hours. Of the two unrelieved patients one was operated for a subacute appendicitis which complicated a duodenal ulcer; the other was unable to retain the tube because of nausea and vomiting. The relief of the pain was associated with an improvement in the patient's nervous state and they were able to secure a night's rest. With the exception of one patient, none of the other patients objected to the presence of the tube.

The six patients with active bleeding ceased bleeding within forty-eight hours with one exception. One man continued to bleed for seventy-two hours.

Examinations of specimens of the gastric contents during the drip treatment showed that the acid had been reduced considerably within one hour. In eighteen cases in which there had been marked hyperacidity, an achlorhydria was produced gradually and on the

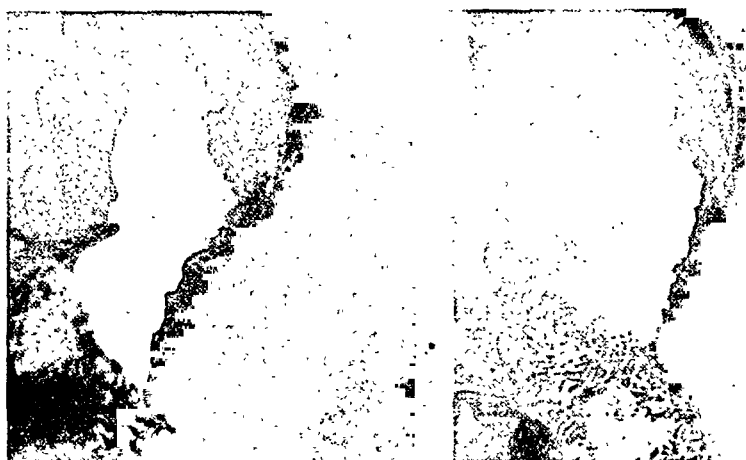


Fig. 1. W. G., age 33. Twelve year history of indigestion. Acute symptoms of pain at night for several weeks. Dietary restrictions and alkaline medication not effective. Pain more or less constant during day. On continuous drip of colloidal aluminum hydroxide for ten days. Relief of pain occurred within four hours after drip started. X-ray on left shows ulcer on lesser curvature before drip started. Film on right taken after ten days treatment with the drip shows the ulcer practically disappeared. There was marked hyperacidity in this case with a nocturnal rise. After four days of the drip there was no free HCl in the secretion. The acid returned to its normal level after aluminum discontinued by drip and orally. Patient observed eight months, no further symptoms.

were given under the skin during the starvation period to these patients who were bleeding.

Pain was the dominant symptom, more or less constant during the day and in the majority (thirty-four of the forty cases) awakened the patient at night. Very little relief was obtained from food or the usual antacids. The majority of these cases were the severe hypersecretive, penetrating type of ulcers, as shown by gastric analyses and roentgen studies. Thirty-four of the forty cases presented a marked hyperacidity and ordinary antacids produced little or no relief when given orally. Examination of the night secretion showed that there was a definite increase in the acidity during the night hours. All but nine of these cases had had adequate treatment of the usual medical type but with poor symptomatic relief.

#### IMMEDIATE RESULTS

All patients with the exception of two were relieved of pain with this treatment. Twenty-six were relieved

third or fourth day of the drip no free hydrochloric acid was present. This continued through the balance of the drip treatment in these cases. After removal of the tube and while the aluminum hydroxide gel was given orally, there was a return of the free acid but it remained somewhat less than previous percentages. Several weeks after the aluminum hydroxide had been discontinued, gastric analyses revealed that the percentage of acid in these cases had again reached approximately the same figures as before treatment; yet the patients were remaining symptom free. In the other patients, reduction in the percentage of acid varied from fifty to eighty per cent during the drip treatment. The neutralization of the acid was gradual and the maximum effect usually was manifest after the third to fourth day of the treatment although the symptoms were relieved in a matter of hours as a rule. The volume of the secretion was also decreased definitely. Yet with this acid decrease, the small feed-

ings of soft foods were apparently handled without difficulty. This reduction in acid figures as manifested during the drip phase of the treatment and afterwards during the ambulatory treatment was in accord with the findings reported by Adams, Einsel and Myers, Jones and Emery and Rutherford. The return of the acid figures toward their normal level, after the aluminum was discontinued was not accompanied by symptoms. Apparently the rapid healing of the ulcer had been effective enough to protect it from the previously irritating effects of the acid.

Twenty-one patients presented evidence of the astringent constipating effect of the alumina gel. In the majority of these, this effect was mild and easily controlled by simple measures. In eight patients the constipating effect was more severe. Two of these were patients with bleeding ulcers, both of whom developed fecal impactions. The bleeding cases were the most prone to show severe constipation. This was undoubtedly partly due to the use of morphine and other

Schmidt and Ivy have shown the effect on absorption from the intestinal tract by colloidal aluminum hydroxide gel. The constipating action is noted by them. Woldman reported the treatment by the drip method of twenty-one cases of hematemesis but made no mention of much trouble from constipation or fecal impaction. Kraemer mentions the constipating effect of aluminum hydroxide in treating peptic ulcer patients. If borne in mind, this problem can be as a rule, easily controlled in the use of the continuous drip.

Roentgen check-up on these patients at the end of the continuous intra-gastric treatment showed in practically every instance definite improvement in the picture. This was manifested usually by a disappearance of the deformity or cessation of the penetration, decrease in the size of the crater, lessened irritability and spasm and a decrease in gastric retention. These changes in the roentgen findings demonstrated the rapidity of the healing process when the acid factor



Fig. 2. C. C., age 50. History of ulcer symptoms of a penetrating type for several weeks. This patient was placed on a Sippy treatment without relief of symptoms. Drip was started and relief obtained in 10 hours. No recurrence of symptoms in 12 months. Drip continued for eight days. X-ray film on left shows ulcer of first portion of duodenum. The film on the right shows a normal appearing duodenal cap two weeks later.

measures designed to put the intestinal tract at rest. Careful watch in such patients must be maintained to prevent possible intestinal obstruction. In those cases in which massive hemorrhage has occurred and the patient is at low ebb in vitality, the use of the continuous drip using the alumina gel is contra-indicated because of its constipating effect. In such cases if it is used at all there should be a greater dilution of the gel and the rate of flow slowed considerably. Sufficient mineral oil should be used through the tube to act as a lubricant and the patient watched carefully. The drip should not be used in the severely debilitated, in those having hypotonicity of the intestinal tract or in those in which some paralysis of the intestine might be suspected. In the average case, however, the constipation is relieved by the regular use of mineral oil, olive oil and occasional oil enemata with very little trouble. The oil is usually given through the tube and may be used several times daily if necessary.

This constipating effect of the alumina gel has not been stressed in other reports but at times it is a definite problem and must be given attention. Beazell,

was continuously controlled day and night. The improvement in the roentgenograms continued during the ambulatory phase. Changes in these findings at the end of the drip treatment are shown in typical cases, as in Figs. 1 and 2.

In addition to the improvement noted in the roentgen findings, clinical improvement was also marked. The general appearance of the patient improved; in most instances their appetite was improved; over half of them gained weight; and their nervous systems became more stable. They could sleep and in each instance, for the first time since the onset of their acute symptoms, felt encouraged about their case.

There were no toxic manifestations and no changes in the patients blood to indicate alkalosis. No evidence of absorption of the aluminum was demonstrated.

#### THE FOLLOW-UP OF THESE CASES

After the intra-nasal tube was removed from the patients, the second phase of the treatment was started. Each patient was then treated as an ambulatory case. The soft diet with in-between feedings of

milk was continued for one month. Belladonna and phenobarbitol was also continued and colloidal aluminum hydroxide gel was given orally. One to two teaspoonfuls in one-third glass of water was given about one hour after each meal and two teaspoonfuls in one-half glass of water at bedtime. Sufficient mineral oil was given to prevent the constipating effects and occasional oil enemas were found to be necessary. After one month of active ambulatory treatment the dietary restrictions were lifted except for red meats, alcohol, highly seasoned foods and tobacco. The medication was discontinued except for occasional doses of the aluminum hydroxide gel orally at bedtime. The patients were observed over the period of time as outlined in the following table.

*Number of treated cases and follow-up by months*

Months	6	8	10	12	14	18
Duodenal ulcers	2	2	2	7	5	5
Gastric ulcers	1	1	2	0	1	2
Jejunal ulcers	0	1	1	0	1	1
Bleeding ulcers	2	1	1	2	0	0

Three patients presented some recurrence of symptoms. One of the patients with a bleeding duodenal ulcer suffered another hemorrhage within six months after the continuous intra-gastric drip was given. One of those with a jejunal ulcer had a return of symptoms within seven months. One of the patients with a penetrating duodenal ulcer developed obstructive symptoms and was subjected to surgery within one year. The remaining patients have remained symptom free with the exception of four cases who developed night pain after the tube was removed. These cases were followed as ambulatory cases during the day, and at night for one additional week we continued the drip with complete relief of symptoms. Two patients did not return for a check-up after six months. Gastric analyses on most of these patients showed that when the aluminum hydroxide is not taken the acid figures are about the same as before treatment. Despite this return to the former acid level in our group of patients, only three had recurrence of symptoms. Only further observation will determine if this return of the acid level means future trouble.

Roentgen examinations have shown continued improvement in the findings in thirty cases which were again rayed at the end of ambulatory treatment of one month. Evidence of healing had continued since the first examination made at the end of the drip treatment.

## CONCLUSIONS

We feel that the continuous intra-gastric drip is of distinct value in the control of gastric acidity in peptic ulcer patients. It offers a means of continuous neutralization of the acid which cannot be adequately obtained by any other method. We have used colloidal aluminum hydroxide by this method in controlling the acid in a group of peptic ulcer patients and have found it a satisfactory agent without any serious side effects excepting a tendency to cause fecal impactions and constipation.

We secured prompt symptomatic relief and both clinical and roentgen evidence of rapid healing of the ulcer in all but two of a group of forty ulcer patients; most of these patients having had little or no benefit from previous medical treatment. It is quite likely that many of these cases would otherwise have been surgical problems because the previous treatment had been so unsuccessful, though considered adequate medically.

It has been in this type of ulcer, resistant to the usual medical management as well as the bleeding ulcer and jejunal or marginal ulcer that we have found this form of treatment most useful. In the bleeding ulcer the continuous control of the acid apparently protects the clot. In those patients with marginal ulcers we have experienced satisfactory results with this treatment in a few cases. This is clinically at variance with the animal experimentation on the use of aluminum hydroxide as recently reported by Fauley, Ivy, et al. The few patients we treated responded favorably. One patient did have a recurrence of symptoms in a few months, but further treatment gave him relief. It is true that the four jejunal ulcer cases treated with the drip did not seem to have an increase in appetite as did the other patients and their weight did not show much change, yet they did improve quite rapidly symptomatically. More patients of this type should be treated before the results can be accurately estimated. It may be that jejunal or marginal ulcers will not respond as well to aluminum hydroxide as other types in which no operative procedure has been performed prior to the treatment.

This treatment appears also particularly helpful in the ulcer patients having night pain associated with nocturnal hypersecretion and acidity. In any ulcer case, it probably would shorten the duration of treatment by hastening the healing process of the ulcer; the only disadvantage being the time required for bed rest in the treatment. We have used it, however, in some of these patients only at night, teaching them to set up the apparatus and pass the Levin tube themselves. During the day the regular ambulatory measures have been followed. This has been successful and the improvement in these cases has been more rapid than in our ordinary methods of management.

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# Etiology of Tuberculous Anal Abscess and Fistula

By

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and

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**THIS** study was made to answer several questions: (1) How many patients in our institution have viable tubercle bacilli in the terminal bowel, and how many of these are infective? (2) Is the tubercle bacillus the primary etiologic agent in the anal abscess or fistula occurring in the patient with pulmonary tuberculosis or is it merely a secondary invader? (3) What is the best criterion for distinguishing tuberculous from non-tuberculous processes of the rectum? To assist in answering these questions a series of 200 cases were studied with particular regard to the bacteriologic and proctoscopic findings.

In a previous investigation we answered as far as possible from a study of our own cases the queries: (1) Should a tuberculous anal fistula be operated upon? (2) How many anal fistulas are tuberculous? (3) How many patients with the pulmonary disease have tuberculous anal fistula? (4) How often has the patient with tuberculous anal fistula tuberculosis elsewhere? and (5) How many fistulas are primary?

## MATERIAL AND TYPES OF PULMONARY DISEASE

In this group of 200 patients the admitting diagnosis was active pulmonary tuberculosis, at the City of Chicago Municipal Tuberculosis Sanitarium. At the time of our examination 171 patients were classified as far advanced, A, B, or C, 24 were moderately advanced, A, B, or C, 3 were minimal, 2 proved to be non-tuberculous.

The patients were those ordinarily referred to the proctologic service. They comprised two groups, those having anal or rectal complaints and those with gastro-enterologic symptoms. The latter were referred by Dr. L. H. Hardt the consultant gastro-enterologist and his staff associates.

## LABORATORY FINDINGS

### Sputum examination:

I. Of the 200 cases studied 84 (42%) had no tubercle bacilli, 116 (58%) had tubercle bacilli in the sputum for three months or more preceding the proctoscopic examination.

### DIRECT SMEARS AND GUINEA PIG INOCULATIONS

The direct smear from the bowel was negative in 128 (64%) and positive in 72 (36%); guinea pig inoculations were negative in 139 (69%), positive in 62 (31%) of the cases.

In the first 100 cases guinea pig inoculations were positive in 40 (40%), while in the second 100 only 22 (22%) were positive, thus indicating the variation in a closely checked series, with no obvious difference in

material or technique and having the same bacteriologic technician present to receive the swabs at the examining table and to make the smears subsequently and carry out personally all the work connected with this series, during the year and a half in which this investigation was made. Thus conclusions drawn from a small series would be rather fallible.

II. Of the 112 cases with a normal mucosa for 24 cm. above the anus and with no peri-anal or peri-rectal disease, the sputum was negative in 53 (47%) and positive in nearly the same number, 59 (52%) Chart 1.

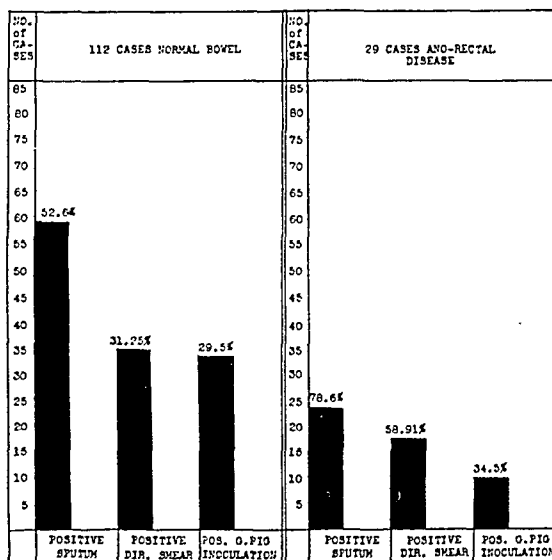


Chart 1

In these grossly normal terminal bowels direct smears were negative in 77 (68%) and positive in 35 (31%), and guinea pig inoculations were positive in 33 (29%).

Thus tubercle bacilli were found in 31% of "normal" rectums, and in 36% of the whole group of two hundred cases.

III. A comparison was made of the cases of normal bowel with those having ano-rectal disease. There was a higher incidence of virulent tubercle bacilli in the patients with abscess, fistula or fissure than in those not having these lesions. Thus, of 112 patients without these peri-anal inflammatory conditions, guinea pig inoculations were positive in only 33 (29%), but in 29 cases having such lesions there were 10 (34%) which were positive.

That is, 34% had infective tubercle bacilli on the mucosa several inches above the local inflammatory

\*From the City of Chicago Municipal Tuberculosis Sanitarium. Submitted July 26, 1939.

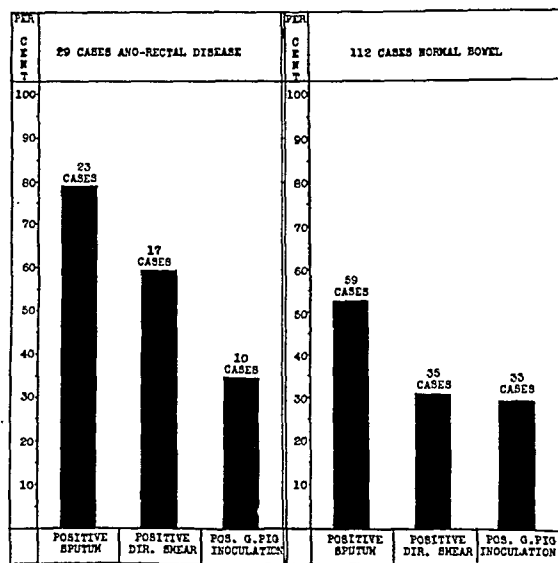


Chart 2

process within two hours after an enema. The evidence here favors the inference that tubercle bacilli caused the abscess or fistula.

We can definitely state from the foregoing data (positive guinea pig inoculations in 29% and 34%, an average of 32%) that a third of our patients have tubercle bacilli in the terminal bowel which are not only viable but capable of causing local disease, e.g., abscess and fistula.

IV. Contrasting laboratory findings in the inflammatory and non-inflammatory cases.

Of patients with inflammatory peri-anal disease, more had positive sputum, 25% as against 20% with negative sputum. Conversely in the non-inflammatory group only 17% had positive sputum but in 25% it was negative.

Direct smears from the bowel mucosa corresponded to the sputum examinations. In inflammatory conditions 23% of these smears were positive, in 19% negative; in the non-inflammatory cases positive smears were found in only 13% but were negative in 22%. Guinea pig inoculations were negative in 22% of the non-inflammatory conditions and positive in only 17%.

Although the above differences are not great, their uniformity strongly suggests that there is some causal relation between the presence of tubercle bacilli in the bowel and anal and peri-anal inflammation. Our culture results did not emphasize the higher incidence of local inflammatory disease, but as stated (see appendix\*) the amount of specimen used readily explains this. Positive guinea pig inoculations did not show as much divergence in inflammatory and non-inflammatory cases as might be expected.

Of the above 29 cases of ano-rectal disease 23 (78%) had positive sputums, only 17 (58%) had positive rectal swabs, and only 10 (34%) were positive on guinea pig inoculation. Chart 2.

This revealed that there was a killing off or dilution of the bacilli while passing through the bowel. It seems more likely the latter. The dilution may be

calculated by comparing the volume of feces to the volume of sputum swallowed.

Of 84 negative sputum cases 10 (12%) revealed positive lesions in the ano-rectal region, indicating a persistence of the infection in this number even after the healing of the lung lesion. It hardly needs emphasis that the removal of such ano-rectal foci of tuberculous infection is particularly important. The focus is readily accessible and elimination is a relatively simple matter.

## DISCUSSION

It has been apparent to many proctologists that there is a definitely higher incidence of ano-rectal disease in the tuberculous than there is in non-tuberculous patients. This is evidenced by 7% of the patients having anal abscess or fistula on admission to the Municipal Sanitarium, whereas the percentage of such cases admitted to a general hospital is very much lower.

And although the great majority, perhaps 90% of anal fistulae in the patients with pulmonary tuberculosis, are tuberculous and usually demonstrably so, the large majority of fistulae in non-tuberculous patients are not caused by the tubercle bacilli and have no relation to tuberculosis. Only 3 to 5% of the cases in the private practice of the senior author are tuberculous.

For some time it has seemed logical that the higher incidence in the tuberculous might well be explained solely on the basis of the increased anal trauma to which these patients are commonly subjected because both diarrhea and constipation are common in their disease and their general condition is poor, and in many cases very poor. There is commonly a diminution in sub-cutaneous adipose tissue and the anal and peri-anal tissues are thus more readily traumatized, especially when hard feces are passed. However, it appears from the foregoing data that more importance should be given to the activity of the tubercle bacillus itself.

We know this: that such lesions as abrasions, small linear tears, etc. of the mucosa and adjacent modified skin at the muco-cutaneous juncture of the anus are the underlying cause and the infection by the local bacterial flora the immediate cause of most abscesses in the region (peri-anal, ischio-rectal, etc.). And it is a well established fact that when virulent organisms of any sort are present they will enter the abrasion and an abscess may result.

When we consider that so many of the patients having the pulmonary disease have tubercle bacilli in the terminal bowel which are both viable and actively infectious, it is logical to conclude that we have real evidence to believe that the tubercle bacillus itself is the important etiologic factor in the higher incidence of ano-rectal disease in the tuberculous.

As this work progressed and it became evident that so many patients had virulent tubercle bacilli in the terminal bowel, the impracticability of using cultural or inoculation methods to determine the character of an abscess or fistula here was forcibly impressed upon us. It is an utter impossibility to wash, or treat tissue excised or curetted from a fistulous tract in any way known to bacteriologists, so that a contamination from viable tubercle bacilli can be positively excluded.

Whatever the original etiological factor in an abscess or fistula about the anus may be, this work has shown the probability of contamination by tubercle bacilli in about a third of our cases. One is familiar with the difficulty of sterilizing the skin of the hands; it may be said that excluding contamination of tissue by the tubercle bacillus in these cases offers comparable difficulties.

There is less possibility of contamination of an abscess than there is of a fistulous tract with patent orifices. The difficulty here is that false positive or negative results may occur. In submitting pus aspirated from an abscess near the anus, we regard a negative report for tubercle bacilli with doubt because whatever the abscess was originally, the usual pus producing organisms may have caused the disappearance of tubercle bacilli. Again a false positive report may follow this pathological sequence; non-tuberculous infection of a crypt or adjacent tissue, but superinfected with tubercle bacilli and these present in the resultant abscess. As there is no way of determining the frequency of this, discussion is rather pointless. It may be said that this is hair-splitting; that whatever it was originally, it is a tuberculous abscess now. This is true.

There is a fact of real importance we would stress: little confidence can be placed in any culture or animal inoculation method for establishing that tubercle bacilli are the cause of anal fistula or abscess communicating with the bowel in tuberculous patients with a positive sputum. Our data clearly indicates the reason and proves such methods of little value. Histo-pathological examination in experienced hands provides the most accurate criteria for distinguishing tuberculous from non-tuberculous processes of the rectum. A discussion of this phase of the subject will be found in a separate article.

### CONCLUSIONS

1. One-third of 200 patients at the Chicago Municipal Tuberculosis Sanitarium had viable, and virulent tubercle bacilli in the lower sigmoidal colon and rectum.
2. Our evidence favors the conclusion that the tubercle bacillus is the primary etiologic agent in the anal abscess or fistula occurring in the tuberculous patient.
3. Because of this high incidence of tubercle bacilli in the terminal bowel, and the consequent probability of tissue contamination, culture and animal inoculation methods are of very little value in establishing the tubercle bacillus as a cause of anal fistula or abscess, in contrast to the real value of histo-pathological examination of tissue.

### APPENDIX—LABORATORY METHODS

The specimens were secured from each patient with sterile 12 inch cotton tipped wood applicators, inserted through the proctoscope, by swabbing the rectal or sigmoidal mucosa which had previously been washed clean by a warm tap water enema. The exudates were swabbed in the relatively small number of cases where these were present.

Smears of the swabbed specimens were made on clean slides and stained for acid fast organisms. An-

other swabbed specimen was put into a sterile tube. The formula used in staining for acid fast organisms was that devised by Ziehl-Neelsen and modified by Cooper (1). The staining technique (2) used was that developed in the laboratory of the Municipal Tuberculosis Sanitarium to meet certain definite requirements necessary in the production of a large volume of routine staining.

At the close of the clinic the specimens were taken to the laboratory and treated as follows:

The cotton tips containing the specimens were carefully removed from the wooden applicators with sterile forceps and dropped into the tubes in which they were collected. Two cc. of sterile physiological saline solutions were added and the mouth of the tubes covered with sterile tin foil.

An hour later the specimens were washed from each cotton tip by forcing the saline solution into the cotton tip by the aid of rubber nipples on the end of sterile Pasteur pipettes, until the specimens were washed out of the cotton.

The saline solutions containing the specimens were transferred to sterile centrifuge tubes, the cotton tips being squeezed against the sides of the tubes with the pipettes in order to get as much specimen out as possible.

The cotton tips were then washed with 2 cc. of 5% oxalic acid in the same manner as with the saline solution and this washing added to the first washings of saline solution. The centrifuge tubes containing the combined washings were covered with tin foil and placed in the incubator at 37.5° C. for 20 minutes. At the end of this time the tubes were removed and each specimen thoroughly mixed with a Pasteur pipette, covered again with the tin foil, and then centrifuged for 25 minutes at 2300 R.P.M. The supernatant liquid was poured off and 2.5 cc. of sterile physiological saline solution was added to the sediment of each specimen and again thoroughly mixed with a Pasteur pipette. The purpose of adding the saline solution after pouring off the supernatant liquid is to have a "carrier" solution containing the centrifuged sediment of the specimen so as to facilitate guinea pig inoculation. \*Approximately 2 cc. of the mixed solution was injected into the left inguinal region of a guinea pig. The remaining 0.5 cc. was cultured for tubercle bacilli. The cultures were examined every ten days and the final diagnosis was made at the end of eight weeks. The culture medium used was that devised by Loewenstein and modified by Jensen (3), and later slightly modified by Holmes (4). A medium composed of a mineral salt solution: potassium and magnesium sulphate, magnesium citrate, asparagin, and glycerine; a starch solution (potato starch); egg fluid (both yolks and whites); and a 2% malachite green solution.

The guinea pigs were sacrificed at the end of eight weeks and studied grossly for tuberculous lesions and for the enlargement of such glands as adrenals, retro peritoneal, inguinal, mesenteric and hilum nodes, characteristic of a tuberculous infection, also any tubercles found in the spleen, liver, lungs and any purulent material from enlarged inguinal glands at the site of inoculation, were smeared and stained for acid fast bacilli.

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## Pectinates, With Special Reference to Nickel Pectinate and Their Therapeutic Value

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AS the result of a number of years' research with pectin, a series of compounds has been developed which have potential value in the medicinal field (16). The compounds referred to are called pectinates, the result of a chemical combination of metals and pectin. One of these compounds in particular, namely, nickel pectinate, has been tested in the laboratory and found to have bactericidal value (1, 13), while being perfectly harmless to the human system (1, 2, 3, 6). Clinical evidence has demonstrated its value in the treatment of various diseases, such as, acute and chronic bacillary dysentery (3); acute ulcerative colitis (7); infected wounds, such as old infected burns, pressure sores, infected soft tissue wounds, osteomyelitis and infected compound fractures (21)†.

Communications with various medical men who have been using nickel pectinate strongly indicate that this product has a wider application in the medicinal field than indicated above, and that it has potential possibilities that have not as yet been investigated.

The purpose of this article is to discuss first: the physico-chemical properties of nickel pectinate and pectinates in general and second: to attempt a correlation between the physico-chemical properties and therapeutic value of nickel pectinate that will aid in explaining the mechanism of the action involved in pectinate therapy.

### THE PHYSICO-CHEMICAL PROPERTIES OF NICKEL PECTINATES AND PECTINATES IN GENERAL

No discussion of pectinates would be comprehensive, without first considering the occurrence, physical and chemical properties of pectin.

Pectin is the intra-cellular cement of cell wall tissue occurring in fruits and succulent edible vegetables. It is found in abundance in such fruits as lemons, oranges, grapefruit, currants, quinces, apples, cranberries and in such vegetables as carrots, turnips, radishes, parsnips and sugar beets. Practically all of the pectin produced commercially is derived from

albedo, the rind and rag of citrus fruit, and apple pomace, the press cake of the cider mill.

Three types of pectic substances are recognized in fruits and vegetables, namely, protopectin, pectin and pectic acid.

Protopectin is the insoluble pectic constituent generally believed to be a compound of pectin and cellulose (20). Pectin is derived from the insoluble protopectin by hydrolysis either with boiling water or preferably under carefully controlled conditions of time, temperature and hydrogen ion concentration which minimize the destruction of pectin. The enzyme protopectinase naturally occurring in the fruit or vegetable will also liberate pectin from the insoluble protopectin. In fact, this enzymic action is accelerated as the fruit ripens and results in a softening of the fruit. In firm, ripe fruit most of the pectin has been liberated from the protopectin. In soft fruits, such as strawberries, raspberries, tomatoes, etc., there is very little protopectin, practically all of the pectic substance is in the form of pectin and its decomposition products.

Pectic acid is a decomposition product of pectin, resulting from the action of the enzyme pectinase. When the fruit becomes overly ripe, most of the pectic substance therein has been converted to pectic acid. Pectic acid may also be formed by the hydrolysis of pectin with either acids or alkalies but more readily with alkalies. In fact, pectin is rapidly decomposed in alkaline media.

From a commercial aspect, the most important property of pectin is its ability to form a jelly when mixed in the proper proportions with sugar, acid and water. Glycerine and other alcohols may be substituted for sugar. Pectic acid in contrast to pectin is insoluble and worthless as a jell-forming substance. Pectin differs from other jell-forming substances in that it is impossible to form a jelly with pectin and water alone. The jelling power of pectin varies considerably, depending upon the conditions of its extraction, maturity of the fruit, variety of fruit used, etc. Pectins up to 500 grade have been made in the laboratory. The term "grade" signifies the number of parts of sugar that one part of pectin will jell under standard con-

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†The "Sardik pectin" and "flake pectin" referred to in Dr. Thompson's article is nickel pectinate.  
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ditions. For example, 100 grade pectin means that one pound of pectin will jell 100 pounds of sugar.

Another important property of pectin is its viscosity which makes it valuable as a stabilizer, emulsifying agent, thickening agent, etc. Doubling the concentration of pectin in water more than doubles its viscosity. Under certain conditions the viscosity of a pectin dispersion is a measure of its jelling power, but it is possible to greatly reduce its viscosity by chemical treatment without lowering its jelling power (17, 18). In general, any hydrolysis of pectin which results in a loss of jelling power is accompanied by a drop in viscosity. Such hydrolysis occurs when pectin is subjected to temperatures above 60° C., the higher the temperature the greater the drop in viscosity. The addition of alkali to a pectin dispersion results in a rapid decrease in viscosity because of the hydrolysis of pectin to pectic acid which imparts no viscosity to water. It is quite probable that the viscosity of pectin and its compounds plays an important role in pectinate therapy, so will be discussed later in more detail.

Pectin is a hydrophylic colloid and has a negative charge. Like most hydrophylic colloids the important factor in its stabilization is its hydration rather than its charge. The charge may be neutralized without coagulation, but a dehydrating agent such as alcohol will coagulate it. On the other hand, a dispersion of pectin in alcohol is possible in the absence of electrolytes. The addition of an electrolyte to the alcoholic dispersion, resulting in a neutralization of the charge, will immediately cause coagulation. Also, the pectin may be precipitated from the alcoholic dispersion cataphoretically at the anode, which is proof that the pectin particle carries a negative charge.

Dry pectin is very difficult to disperse. When introduced into water the particles hydrate on the surface forming thereon a gummy coating which slows down the imbibition of water and thus decreases the rate of hydration. Other dry pectin particles stick to this gummy coating and result in the formation of a lumpy, slimy mass which is difficult to break up. This difficulty has prevented the household use of dry pectin in making jams, jellies and marmalades and has necessitated the dispersion of pectin for such purposes in the form of a water dispersion (approximately 4%) in sterile bottles. Mechanical mixtures of powdered pectin with such things as sugar and salt are being used to aid in the dispersion, the principle involved being the separation of the particles of pectin so that they will hydrate before coming in contact with each other. The formation of certain pectinates will result in a product which is readily dispersible even in cold water. This will be discussed later.

The chemical composition of pectin varies over a wide range depending upon the nature and amount of hydrolysis that has occurred up to and during the isolation of the pectin from the raw material. When stored under certain conditions, a slow hydrolysis may also occur with a subsequent drop in grade and viscosity. However, the various components which together make up the pectin molecule have been identified beyond any question of a doubt. Von Fellenberg (12) and Ehrlich (8, 9, 10, 11) have made notable contributions to the chemistry of the pectin molecule and Ripa covers the subject rather thoroughly in his book on pectin (19).

Accordingly, it is well agreed that the pectin molecule consists of galacturonic acid, arabinose, galactose,

methoxyl and acetyl groups. The nucleus of the molecule is a polymer of galacturonic acid, some say the tetra-acid, others the octa-acid, while a few think it is considerably higher than the octa-acid. It is not necessary for the purposes of this discussion to present arguments pro and con, but to simplify the situation it will be assumed that the nucleus of the molecule is the octa-acid since there is strong evidence that it cannot possibly be the tetra-acid (18). Since the molecules of the galacturonic acid are combined through their aldehyde and hydroxyl groups, the eight carboxyl groups are free and available for chemical reaction with other substances. In nature usually seven of the eight carboxyl groups are esterified with methyl alcohol, leaving only one free carboxyl group. One molecule each of arabinose and galactose and two acetyl groups are attached to the octa-galacturonic acid through the hydroxyl groups of the acid.

According to this description, unhydrolyzed pectin is monoarabino-mono-galacto-diacetyl-heptamethoxyl-octagalacturonic acid and contains the following percentage of the various constituents (18):

	Per Cent
Galactose	9.65
Arabinose	8.04
Acetic acid	6.43
Methoxyl (CH <sub>3</sub> O)	11.63
Galacturonic acid	83.17

It is, however, impossible to obtain pectin in the unhydrolyzed state so naturally it will vary considerably in its chemical composition. Myers and Baker (18) have shown that the chemical composition of pectin varies considerably with the method employed in the extraction of the pectin. While varying the temperature from 60° C.-100° C.; the pH from 0.2-3.0 and the time of the extraction from 0.5-4 hrs., the percentage of the constituents varied as follows: galactose, 0.05%-6.43%; arabinose, 3.01%-7.73%; acetic acid, 1.90%-4.73%; methoxyl, 7.59%-12.35%; galacturonic acid, 87.21%-95.18%.

The hydrolysis of pectin may be divided into two classifications, namely, destructive and constructive. Destructive hydrolysis involves a depolymerization of the octa-galacturonic acid with a subsequent rapid drop in viscosity and grade. The end product of this hydrolysis is pectic acid which in reality is tetra-galacturonic acid. Destructive hydrolysis occurs rapidly in alkaline media at room temperature and completely de-esterifies the pectin as well as converting it to pectic acid. In fact, the saponification of pectin with alkali is used for the quantitative estimation of its methoxyl and pectic acid content.

Destructive hydrolysis occurs also when pectin is heated with a strong acid, such as hydrochloric. The pectin may be completely de-esterified and broken down to pectic acid, as occurs with alkali, but heat is required for a comparatively long period of time. By regulating the quantity of acid used in the hydrolysis, various reactions may be obtained. For example, by heating pectin with approximately 2.5% sulphuric acid for a long period of time, the pectin is completely depolymerized to crystalline galacturonic acid (14). Distillation with 12% hydrochloric acid under a reflux condenser results in a complete decarboxylation of the pectin with a quantitative evolution of carbon dioxide and partial conversion to furfural.

Destructive hydrolysis also occurs by the action of the enzyme pectinase. Generally speaking, destructive hydrolysis in acid or neutral media starts at a temperature of approximately 60° C. and is accelerated as the temperature is increased. The practice of autoclaving pectin to produce a sterile product should be discouraged because of the rapid destruction or depolymerization of the octagalacturonic at such elevated temperatures.

Destructive hydrolysis, resulting only in depolymerization of the octa-galacturonic acid into the tetra-acid without de-esterification or removal of arabinose, galactose or acetyl groups may be accomplished by refluxing pectin with distilled water (18). It is thus possible to completely destroy the jellying power and viscosity of pectin without de-esterification or conversion to a product insoluble in water.

Constructive hydrolysis involves a reduction in the size of the pectin molecule without depolymerization of the octa-galacturonic acid. This constitutes a partial de-esterification and partial removal of galactose, arabinose and acetyl groups from the octa-acid with a subsequent reduction in viscosity but not in grade. In fact, the grade is actually increased because the jellying power of pectin is due solely to the octa-galacturonic acid content and the removal in part of the other constituents increases the percentage of the octa-acid. This type of hydrolysis is constructive in the sense that it produces a pectin product of different chemical and physical properties which for definite purposes are beneficial. For example, a partially de-esterified pectin produces a much more elastic jelly and requires a longer time to set. In jelly parlance this type of pectin is called a "slow-set pectin."

Since constructive hydrolysis results in a partial de-esterification of the octa-galacturonic acid, a corresponding number of carboxyl groups are liberated with a subsequent increase in the combining power of pectin, thus making it possible to precipitate the hydrolyzed product with certain metals which will not ordinarily precipitate pectin. This process is being used to some extent in the manufacture of pectin for its recovery from dilute extracts, and results in a product differing greatly in chemical composition from that of ordinary pectin, yet the term "pectin" includes both products.

As previously stated, destructive hydrolysis with acids occurs at temperatures above 60° C. Constructive hydrolysis is accomplished with acid at temperatures below 60° C., the amount of hydrolysis depending upon the hydrogen ion concentration, time and temperature during the hydrolysis. For example, 196 grade pectin having a viscosity of 10 and methoxyl content of 9.54 was dispersed in water acidified with hydrochloric acid to a pH of 0.8 and heated for 50 hours at a temperature of 40° C. At the end of 50 hours the pectin was recovered from the dispersion by precipitation with alcohol. The analysis of the alcohol precipitate showed that the viscosity and methoxyl content had dropped to 6.89 and 7.59% respectively, while the grade had increased to 254. The increase in grade was due to the fact that a partial removal of arabinose, galactose, methoxyl and acetyl groups increased the percentage of octa-galacturonic acid in the pectin which is responsible for the jellying power of the pectin. The increase in elasticity of the jelly made from this pectin also contributed to the rise in grade. The drop in viscosity from 10 to 6.89 was due to a re-

duction in the size of the pectin molecule as a result of the partial removal of the various constituents from the octa-acid nucleus. This is in accordance with Stoke's law.

The fact that the grade of the pectin was not lowered during the hydrolysis under the above conditions means that no depolymerization of the octa-acid occurred and that the water holding capacity of the pectin was unimpaired.

The chemical composition and physical properties of pectin may be varied over a wide range by subjecting the pectin to constructive hydrolysis and varying the time, temperature and hydrogen ion concentration of the hydrolysis. In general the lower the pH the more effective is the removal of methoxyl groups which liberates a corresponding number of carboxyl groups which are available for chemical combinations.

Pectin is a colloidal acid and when reacted with certain metallic salts forms pectinates. If the quantity of metal reacting with the pectin is controlled, the colloidal properties of the pectin are fully retained and the resulting product, a pectinate, is in reality a colloidal salt which needs no peptizing agent to stabilize it. Metallic colloids in the medicinal field have so far found only a limited application, confined mainly to external uses because of their toxicity to the human system. They usually consist of an insoluble metal or metallic compound which in itself is not colloidal, but requires the addition of a peptizing agent to affect dispersion. For example, there are several colloidal silver preparations on the market which consist of finely divided metallic silver or some insoluble compound thereof, such as silver oxide, which will not remain in the dispersed state and require a peptizing agent such as proteins to stabilize them. Various factors influence the stability of such colloidal dispersions, such as light, temperature, hydrogen ion concentration, etc., so that their bactericidal value usually decreases with age. When any substance comes in contact with the dispersion that ordinarily will dissolve the insoluble silver therein, such as acid, a crystalloidal salt is formed, resulting in increased ionization of the silver with a subsequent increase in toxicity.

Proteins are amphoteric and have an isoelectric point, approximately at a pH of 4.2. Above a pH of 4.2 they can combine with metals because of their carboxyl groups, below a pH of 4.2 they can combine with acids because of their amino group. Proteinates may be formed by reacting metallic salts with proteins at pH's above 4.2. However, as acid is added to a proteinate and the pH approaches the isoelectric point, more and more metal is liberated. At the isoelectric point no metal is combined with the protein and the metal therein is converted to a toxic salt. Consequently no proteinate of a toxic metal can be taken internally because of the instability of the compound at the low pH's in the stomach, which results in a liberation of the toxic metal.

In contrast to protein, pectin is not amphoteric and does not have an isoelectric point. It cannot combine with acids but can combine with metals forming pectinates which are very stable in acid media. Certain pectinates are so much more stable than proteinates that pectin will remove certain metals from proteinates. This fact greatly reduces the possibility of any

cumulative toxic effect of metals in the human body when taken internally in the form of pectinates.

When certain metals, in particular, copper, nickel, lead, iron, aluminum, manganese, cadmium, calcium and magnesium, in the form of soluble salts, are added to a pectin dispersion, an abnormally high viscosity results. The increase in viscosity varies with the nature and amount of metal added, also with the hydrogen ion concentration. When added in excess certain metallic salts will coagulate pectin.

According to von Fellenberg (12) copper sulphate, lead nitrate, basic and neutral lead acetate, ferric chloride will precipitate pectin. He lists the salts that will not coagulate pectin as follows: silver nitrate, mercuric chloride, cadmium nitrate, nickel sulphate, ferrous sulphate, cadmium chloride, zinc sulphate, manganous chloride, calcium chloride, strontium chloride, barium chloride and the alkali salts. The salts that will precipitate pectic acid are listed by von Fellenberg as follows: calcium chloride, strontium chloride, barium chloride, magnesium chloride, aluminum chloride, ferrous sulphate, ferric chloride, copper sulphate, cobalt nitrate, nickel sulphate, cadmium chloride, zinc sulphate, stannous chloride, manganous chloride, silver nitrate, lead nitrate, and he also states that mercuric chloride will not coagulate pectic acid. Hydrogen ion concentration plays an important role in the precipitation of pectin with metals, a factor which von Fellenberg failed to take into consideration in his experiments with pectin.

Pectic acid is completely de-methylated pectin in which all of the carboxyl groups are free and available for combination with metals, consequently it can combine with a much greater quantity of metal than can pectin, which in most cases is sufficient to precipitate the pectic acid. In other words, many of the metals that will precipitate pectic acid will not precipitate pectin due to the fact that pectin cannot combine with a sufficient amount of these metals to cause insolubility because most of its carboxyl groups are methylated. As pointed out by von Fellenberg, the more methoxyl groups removed from the pectin molecule, the more carboxyl groups become available for reaction with metals and the easier the precipitation with metallic salts. Until recently no method was known by which pectin could be de-esterified without at the same time depolymerizing the octa-galacturonic acid and thus destroying its jellying power. As a result of research at the Delaware Agricultural Experiment Station (18) a method was devised whereby pectin could be at least partially de-esterified without depolymerization (constructive hydrolysis) thus making it possible to precipitate pectin with some metals that ordinarily would not precipitate pectin, and at the same time retaining its full jellying power.

However, from a bactericidal and therapeutic point of view, the pectinates containing sufficient metal to cause coagulation and loss of colloidal properties are of very little value.

It has been found that the addition of small amounts of certain metals to pectin intensifies its colloidal properties. For example, if a small amount of nickel sulphate is added to a pectin dispersion, the viscosity is increased. This is due to the fact that the nickel pectinate formed hydrates to a much greater extent than pectin, and as a result the particle swells and becomes larger and less dense. According to Stoke's law, the viscosity of a colloidal dispersion increases

with the size of the particle. The amount of hydration of the nickel pectinate depends upon the hydration ion concentration of the dispersion. If acid is now added to the nickel pectinate, the viscosity may be reduced to that of the pectin before the addition of nickel sulphate, not because the acid removes the nickel from the pectin, but because of the reduced hydration at the reduced pH. The viscosity may be again increased at this reduced pH by the addition of more nickel or by raising the pH by the addition of an alkali. In this respect nickel pectinate differs from pectin which always shows a reduction in viscosity upon addition of alkali or increase in pH. This may be an important factor in pectinate therapy.

When a nickel salt is added to a pectin dispersion in increasing amounts the viscosity increases up to the point where the pectin has combined with all the nickel possible. At this point ordinary pectin, not submitted to constructive hydrolysis, will contain approximately 1.2% combined nickel. If nickel pectinates are prepared containing various percentages of combined nickel up to 1.2% nickel and separated from the water either by precipitation with alcohol or dried on a revolving heated drum, the dispersibility of the dry products in water will increase as the percentage of nickel increases to 0.5%. In fact, a pectinate containing only 0.3% of combined nickel will hydrate immediately and completely as it comes in contact with water without forming any lumps. The hydrated gelatinous particles will disperse readily with slight agitation even in cold water. The rate of hydration of pectinates is accelerated as the combined nickel is increased from 0.5% to 1.2%, but the gelatinous particles become a little more difficult to disperse but will do so upon heating, or upon the addition of a small amount of acid. Nickel pectinate will disperse in acid media just as readily as in distilled water, but in excessive acidity media requires slightly more nickel to maintain the rate of dispersion. Calcium and magnesium pectinates disperse fairly well in distilled water, but not in the presence of acids, due to their instability in acid media or to decreased hydration because of the reduced pH. All pectinates do not disperse more readily than ordinary pectin, in fact, very few of them have any appreciable advantage over pectin in this respect. Copper pectinate hydrates readily but the swollen gelatinous particles are difficult to disperse. From a dispersible standpoint such pectinates as copper, lead, silver, manganese, zinc, cobalt, etc., should each contain sufficient nickel to disperse without difficulty.

When powdered pectin is placed on the surface of water there is no movement of the particles over the surface, the powder remains stationary in one clump. However, if powdered pectin is triturated in a mortar with dry nickel sulphate so that the nickel therein is about 0.5%-0.6% of the weight of the mixture, and this mixture is placed on the surface of water, the particles will fly apart and spread themselves rapidly over the entire surface of the water, at the same time they will hydrate 100%. This indicates an intensification of the charge on the colloidal particles so that they repel each other and fly apart, resulting in a much more stable colloid than pectin itself. An intensification of the charge on the particle would naturally increase the absorptive capacity of the colloid which may be an important factor in detoxification.

## NICKEL PECTINATE THERAPY AND POSSIBLE EXPLANATION OF ACTION INVOLVED

Block (3) in his report on pectin and nickel pectinate in acute and chronic bacillary dysentery shows very conclusively that pectin per se is of no value in the treatment of this disease. He states that the diarrheal symptoms continued practically unabated in every case during the entire course of the treatment with pectin. He concludes that "granular or pure pectin did not exhibit a favorable effect. There was no reduction in temperature and the course of the disease was either unaltered or adversely affected, toxemia being marked throughout. Bloody diarrhea occurred frequently. It is apparent, therefore, that this substance does not possess any detoxifying properties."

In contrast, nickel pectinate according to Block possesses detoxifying bactericidal and anti-hemorrhagic properties, proven to be effective in the treatment of bacillary dysentery, and observed "a definite improvement in every patient in the appearance and general condition accompanied by the disappearance of all acute symptoms, tenesmus and bloody diarrhea and an increase in weight."

The "pure pectin" used by Block was the same type of pectin employed in the manufacture of the nickel pectinate which he used. No beneficial results were obtained with pectin but when the same pectin was converted to nickel pectinate by the addition of approximately 0.3% nickel, a decided improvement in the patient was noted.

Due to a lack of sufficient data, any attempt to explain the value of nickel pectinate in contrast to that of pectin in the treatment of bacillary dysentery is purely a matter of conjecture. However, there are certain established properties of nickel pectinate that certainly have some bearing on its therapeutic value. Of primary importance is its bactericidal value.

### BACTERICIDAL VALUE OF NICKEL PECTINATE

Tompkins (13) found that all the pectins which he tested as well as pectic acid and methyl d-galacturonate actually promoted the growth of bacteria. In contrast, nickel pectinate manifested bactericidal action which varied with the percentage of nickel present. He found that the bactericidal action was more marked after autoclaving the nickel pectinate and that its activity decreases at pH's above 5.5.

Arnold (1) also found that pure pectin accelerates the growth of bacteria while in contrast nickel pectinate inhibits the growth of bacteria, its inhibiting action decreasing as the pH is increased. The autoclaved samples exerted greater bactericidal action.

It has long been known that certain metallic ions, nickel included, are toxic to bacteria. It is safe to assume, therefore, that the inhibiting action of nickel pectinate on the growth of bacteria is due to ionization of the nickel. That the ionization is slight is proven by the fact that nickel pectinate did not completely destroy the bacteria but simply retarded their growth. Nickel pectinate ionizes to a greater degree as the pH is decreased, hence its increased bactericidal activity at reduced pH's. Near the neutral point there is scarcely any ionization and as a consequence no activity. All metallic pectinates do not exhibit the property of decreasing toxicity to bacteria with in-

crease in pH because acids do not have the same effect on the ionization of all metallic pectinates.

Both Arnold and Tompkins observed an increase in the bactericidal value of nickel pectinate after autoclaving. As previously mentioned, destructive hydrolysis, resulting in depolymerization, is greatly accelerated at autoclave temperatures, resulting in an eventual breakdown to nickel pectate if continued for a sufficient length of time. Nickel pectate is not dispersible in water. However, a small amount of acid will remove the nickel from this compound very easily resulting in the formation of insoluble pectic acid and a soluble nickel salt which ionizes to a much greater extent than does nickel pectinate. Any degree of depolymerization of nickel pectinate will result in a decomposition product somewhere between nickel pectinate and nickel pectate which is less stable in acid media, and consequently results in a higher concentration of nickel ions. It is, therefore, natural to expect that autoclaved nickel pectinate would have a greater bactericidal action than unautoclaved nickel pectinate. Since jellying power or grade depends upon the degree of polymerization of the pectin molecule, the bactericidal value of nickel pectinate increases as the grade decreases, but the nickel pectinate becomes less stable in acid media.

The hydrogen ion concentration of a colloidal acid is proportional to its concentration. Colloidal salts ionize in a similar manner so that the higher the percentage of nickel combined with the pectin and the greater the concentration of nickel pectinate the greater the bactericidal action because of the increase in the nickel ion concentration. This is in accordance with the findings of Arnold and Tompkins.

The bactericidal activity of nickel pectinate beyond doubt is beneficial in the treatment of bacillary dysentery, but since the bacteria are not completely destroyed, there must be some other contributing factor that is responsible in a large measure for its beneficial effect. Arnold (1) has called attention to this as follows: "The intra-intestinal bactericidal action is not clearly understood. The clinical improvement of bacillary dysentery patients administered nickel pectinate by mouth manifest clinical improvement out of proportion to the demonstrable in vitro bactericidal power of the nickel pectinate." There is a possibility that the catalytic activity of nickel may play an important role in nickel pectinate therapy.

### NICKEL PECTINATE AS A CATALYST

The catalytic activity of nickel has been utilized for many years in the chemical industry for promoting and accelerating chemical reactions. One of the well-known applications is the use of nickel as a catalyst in the hydrogenation of vegetable oils. When attempting to postulate a theory explaining the total therapeutic value of nickel pectinate one must at least take into consideration this important property of nickel.

Theoretically, under certain conditions, pectin should be able to combine with proteins, but since Block (3) observed no detoxifying action of pectin in patients suffering from bacillary dysentery, it is evident that no appreciable amount of toxic proteins combined with the pectin. It is quite possible that with nickel attached to the carboxyl groups of pectin the combination of pectin and proteins is accelerated, ac-

counting in part for the detoxifying action of nickel pectinate observed by Block.

The catalytic production of antitoxin and agglutinin by nickel pectinate is not beyond the realm of possibility. In fact, there is some evidence to this effect. The Drinkers (5) published an extensive report on the Hygienic Significance of Nickel, which contains an abstract of two articles one by Walburn (22) and the other by Madsen (15) which are pertinent. Walburn shows that "the chlorides of manganese, cobalt, nickel and zinc augment the production of agglutinin and antitoxin in the goat and in the horse when these animals have been injected with the colon and the diphtheria bacillus respectively. The amounts of salts used in the experiments were: for the goat, 25 cc. of a 0.01 molecular solution; for the horse, 10 cc. of a 0.5 molecular solution, calculated as hydrates. The salts were injected intravenously in single daily doses."

"Madsen determined that daily injections of 0.5 gm. of the chlorides of manganese, zinc, nickel, cobalt, and other metals into goats that had previously been immunized by specific agents served to maintain the antibody content of the blood at a high level. Similar results were obtained with the horse immunized against diphtheria. The author suggests that antibody formation is a secreting process and that the action of the metals is in the nature of a catalytic effect on enzyme processes."

Hans Zinsser in his textbook on bacteriology states: "The blood-serum of newborn guinea-pigs hardly ever contains agglutinin for *B. coli*, while that of adults acts upon these bacilli in dilutions of 1:20. Similarly, infants show lower normal agglutinating values than adults." Diarrhea in an infant is a much more serious proposition than in an adult because the infant is not immunized against this disease. However, infantile diarrhea responds very rapidly to nickel pectinate therapy, all symptoms disappearing generally within forty-eight hours. Is this not due in part to the rapid formation of agglutinin and antitoxin by the catalytic action of the nickel pectinate?

Block (3) states: "Nickel pectinate administered every three hours will tend to facilitate continuous effect for which the preparation is given. It will promote early healing, and may prevent recurrences. Upon recovery, the patient should receive for some period of time a reduced dose of nickel pectinate in order to rid the system of residual remains of the disease."

Madsen, as previously quoted, has shown that daily injections of small amounts of metallic salts served to maintain the antibody content of the blood at a high level. Block has recognized the necessity of administering a reduced dose of nickel pectinate after the apparent recovery of the patient from a severe case of

bacillary dysentery. Antibodies undoubtedly disappear from the intestines at a much faster rate than they do from the blood and since nickel pectinate does not depopulate the intestines it seems logical that nickel pectinate should be administered in small doses just so long as any bacilli still remain in order to maintain the antitoxin.

If nickel pectinate does stimulate the production of antitoxins in the body, then there are a large number of applications that only the medical profession can visualize. Arnold (1) observes that metal pectinates have different action on various bacteria. Perhaps different metallic pectinates are also specific in their production of antitoxins.

Nickel pectinate aids in the assimilation of vitamins probably due to catalysis. Eddy (7) reports a case of acute ulcerative colitis in which he cooperated with Dr. Thomas Mackie at Roosevelt Hospital in which nickel pectinate brought about recovery when all other means had failed to do so. Before ingestion of nickel pectinate the blood A and C of the patient was 1.5 mg. % and 0.10 mg. % respectively; after ingestion of nickel pectinate the blood A and C rose to 4.0 mg. % and 1.65 mg. % respectively.

Chen (4) states: "In  $B_1$  deficient rats, the addition of 'Nipectin' appears to have a synergistic action with  $B_1$  in increasing the body weight of experimental animals." Chen did not observe any beneficial results in connection with Vitamin D.

#### OTHER METALLIC PECTINATES

Arnold (1) has presented data on the bactericidal action of pectin and pectates of nickel, cobalt, manganese, lead, zinc, copper, calcium and silver. His results show that pectin and calcium pectinate do not possess bactericidal power. Of the other pectinates, silver exerted the greatest bactericidal action, followed by cobalt, copper and nickel in order. Copper pectinate was found to be more toxic for *Staphylococcus aureus* than any other metal pectinate studied. With this one exception silver pectinate exerted the most marked bacterial killing power.

There is very little clinical evidence on the metallic pectinates with the exception of nickel, because of the newness of the products. Silver pectinate, because of its outstanding bacterial killing power has been tested to some extent as a substitute for various other colloidal silver compounds now on the market with very encouraging results. The work is progressing rapidly and should be available for publication in the near future. Silver pectinate has been used by one doctor in particular with marked success in the prevention of post-operative infections by impregnating dressings, in the treatment of athletes foot and certain chronic forms of skin diseases.

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# Gastro-Intestinal Pseudoleukemia

## (Report of Case)

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THE following case report is presented because of the unusual physical and roentgenological findings. Included in the conditions considered in diagnosis, gastro-intestinal pseudoleukemia and polyposis of the small intestine are rare diseases. The symptomatology and findings in these diseases are only inadequately described in medical literature, and no roentgenological pictures similar to those observed in this patient could be found. Following the case report there is presented a discussion of the literature of the above named conditions; the reasons for the interpretation of the roentgenological findings is given and the clinical features are discussed.

### CASE HISTORY

S. P., a single white male, aged 32 years, entered the Sanatorium October 21, 1938. The patient did not consider himself ill and objected to examination which the Sanatorium requires of all incoming patients. On questioning he admitted a loss of sixty pounds in weight in the two years prior to his admission. At that time tonsillectomy was done in an attempt to relieve frequent "colds" and following this operation the patient had an episode extending over several weeks during which there was loss of appetite, crampy abdominal pain, and constipation alternating with diarrhea. Since this episode the patient continued to have poor appetite and had taken two rest periods in an attempt to regain the lost weight, without success.

Direct questioning regarding digestion at the time of admission brought out the fact the patient frequently had a sensation of fullness and weight after meals, but he insisted stools had been normal for the past year with one small rather constipated stool at night and a somewhat soft mushy stool early in the morning. There were no other complaints. The patient denied use of alcohol, and dietary habits were very good.

Physical examination revealed marked emaciation, dry skin, slight clubbing of the fingernails, pallor of the conjunctivae. The eyes, ears, nose and sinuses were normal. The mucous membranes of the mouth were pale, the tongue large without other abnormality, teeth were in good condition, and the tonsil beds were clean. The heart and lungs were not grossly abnormal, peripheral arteries soft, systolic blood pressure 104, diastolic 70. The abdomen showed a typical "pot belly." It was distended and tense, tympanitic in the center, and dull in the flanks. At the first examination the liver could not be felt. At later examinations, with less abdominal distension, the liver was easily palpable—the lower edge on a level with the umbilicus. The feet and ankles showed a grade one pitting edema.

Clinical laboratory findings were as follows: Urine analyses, 10-31-38: morning specimen, 240. cc.; appearance slightly cloudy; color amber; reaction alkaline; specific gravity 1.014; albumin 0; sugar 0; acetone 0;

urobilinogen markedly increased. Microscopic—rare erythrocyte, occasional leucocyte, occasional round and squamous epithelial cells. 11-1-38: morning specimen, 280. cc.; appearance clear; color lemon; reaction neutral; specific gravity 1.018; albumin 0; sugar 0; acetone 0; urobilinogen markedly increased. Microscopic—occasional leucocyte, occasional squamous epithelial cells, no erythrocytes seen, inorganics, few urates. Blood cytology: 10-31-38: erythrocytes 3,700,000; hemoglobin 9.7 grams (67%); leucocytes 4,800; neutrophils 0-3-45-27; eosinophils 1; basophils 1; monocytes 1; lymphocytes 22. Description of smear—anisocytosis of red blood cells, many hypochromic macrocytes. 11-1-38: leucocytes 5,700; neutrophils 0-1-51-27; monocytes 1; lymphocytes 20. 11-21-38: erythrocytes 4,080,000; hemoglobin 11.8 grams (80%); leucocytes 5,000; neutrophils 0-0-40-15; eosinophils 3; monocytes 8; lymphocytes 34. Blood chemistry: 11-3-38: free cholesterol 112.7 mgm. %; cholesterol esters 72.5 mgm. %; total 185. mgm. %. 11-4-38: plasma fibrinogen 0.59 mgm. %. Albumin 3.17 mgm. %. Globulin 2.05 mgm. %. Albumin-globulin ratio 1.54. Erythrocyte sedimentation rate, 11-2-38: 59 mm. in 1 hour, Westergren method. Galactose tolerance test, 11-5-38: 3.6 grams excreted in 4 hours. Gastric analysis, 11-2-38: free hydrochloric acid absent, total acidity 1-2. Feces, 11-2-38: appearance soft, unformed, light yellowish-brown color, few gross food particles; reaction acid; occult blood negative; fat 0; starch few digested granules; muscle fibers rare, well digested; ova and parasites, none seen; no leucocytes seen; no erythrocytes seen. 11-10-38: (after Schmidt Intestinal Test Diet) appearance fatty, unformed slightly foaming specimen of slightly reddish color; reaction slightly acid; fat, very little; starch digestion quite normal; muscle fibers poorly digested, striations very marked; urobilinogen present. In spite of the poor Sudan reaction the amount of fat appears very markedly increased. Urinary amylase test, 11-2-38: 32 units.

Special examinations: tuberculin intradermal test positive to 0.1 mgm., O. T. Proctosigmoidoscopy, no pathology visible in rectum or sigmoid. Roentgenological studies will be presented in detail because of the unusual findings encountered.

X-ray findings: esophagus is normal. The stomach shows no abnormality in size, position, or movements, no filling defects are observed even with close observation of the mucosal picture. The contrast meal passes without delay into the duodenum and rapidly through it. It shows a well defined semi-circular filling defect in its upper right lateral contour. The jejunum shows many small, circular, radio-translucent areas one-half to one centimeter in diameter. All are very sharply outlined. These areas are so numerous they appear to replace all of the normal mucosa. They give to the small intestine a honey-combed appearance throughout. In addition, there are numerous niche-like formations one-half to one and one-half centi-

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Submitted July, 1939.



Fig. A. Photograph of intestine in case of intestinal pseudoleukemia from Ewing's "Neoplastic Diseases." Courtesy W. B. Saunders Company.

meters in diameter some of which are pedunculated. The honey-comb pattern is observed in some of the larger niches. The filling defects decrease in distinctness as the cecum is approached. In the latter region one can see numerous folds in addition to filling defects. At the end of three hours the contrast meal is massed in the pelvis with its head in the ascending colon. Flecks of barium remain throughout the small intestine. The contour of the ascending colon shows filling defects similar to those described above. The six hour film shows greater definition of the defects. There is a diverticulum-like niche about two centimeters in diameter in the median contour of the ascending colon. The ascending and transverse colons are large and the mucous membrane appears thin and atrophic. The sigmoid is redundant with large loops reaching up to the splenic flexure. The lower end of one of these loops shows an irregular-shaped filling defect. Evidence of honey-combing, though less distinct than is observed in the small intestine, is shown throughout the descending colon and sigmoid. At twenty-four hours, the outlines of the ascending colon are well defined. The lower part of the ascending colon shows scattered, circular shadows which appear to be the result of the contrast meal left in the diverticula. The sigmoid is only partly filled. Most of the contrast meal is in the rectal ampulla. The shadow of the liver is enlarged, reaching down eight centimeters below the 11th rib.

Discussion of the X-ray findings: There can be little doubt that the peculiar picture just described is caused by the protrusion of small and large nodules into the lumen of the intestines. They are very tightly packed, particularly in the proximal part of the jejunum where they appear to occupy the whole in-

testinal wall. The small diverticula which can be seen in various parts of the small and large intestines may be either congenital or, what seems more probable, they may be secondary to distentions of the intestinal wall which has been weakened by nodular growths. The distribution of these nodes is remarkable. They could not be seen in the stomach despite careful study of the mucosa; in the duodenum only one circular filling defect appears. They occupy the proximal part of the small intestine; they become fewer in number in the ileum, colon and sigmoid; but in the colon or sigmoid one can see many areas which show the same kind of honey-combing which appears in the jejunum though less distinctly. Another point which seems worthy of attention is the peculiar, paper-thin appearance of the walls of the colon and sigmoid. They appear atrophic even in places where no evidence of node formation can be found.

What are these nodes? The first impression is one of widespread polyposis of the small and large intestines. The pictures resemble to a great degree the numerous X-ray publications of polyposis of the large intestine and sigmoid. However, the literature on polyposis of the small intestine is far less extensive and conclusive.

Müller (1) discusses the aspects of general intestinal polyposis, without stating in what percentage of his cases the small intestine was involved.

Hauser and Kauffman (2) (cited by Ewing) observed polypoid involvement of the entire mucosa from pylorus or cardia to anus, but the exact histological nature of the polyps in their cases is not evident from Ewing's quotation.

Talia and Picara (3) state that polyposis of the intestines occurs in the following order of frequency:



Fig. 1. Film made ten minutes after ingestion of barium sulphate.



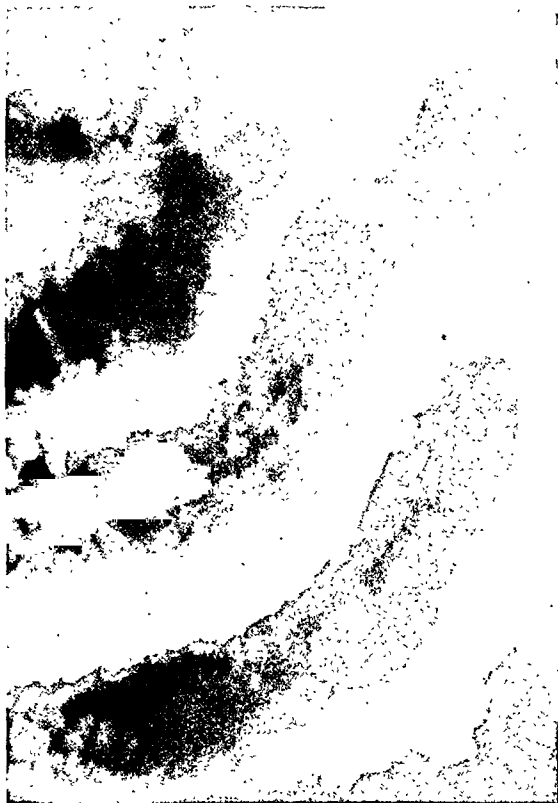


Fig. 2. Roentgenogram of small intestine ten minutes after oral administration of barium sulphate meal showing honey-comb appearance. (Enlargement of Fig. 1).

rectum, sigmoid, stomach, duodenum, terminal ileum, jejunum and ileum.

Gatersleben (4) reports a case of polyposis of the small intestine which shows diffuse involvement of the jejunum and parts of the ileum. The patient was operated several times for this condition which caused invagination and gangrene of the intestines. There were numerous polyps present, the histological picture of which changed from benign adenopapilloma to cancerous growths in the course of several years. The photograph of a specimen obtained by resection shows various polyps of the mucosa of the small intestine, some are pedunculated, others have a broad base. The picture described by Gatersleben differs somewhat from the findings in cases where the nodes are very tightly packed. In our roentgenograms no trace of Kerkring folds can be seen in the proximal parts of the small intestine, whereas, Gatersleben's specimen shows many folds in the ample space between the tumors.

Other reports of polyps of the small intestine (German (5), Santer (6), Talia and Picara (3)) concern single polyps which caused various surgical conditions as invagination, occlusion, etc. All publications stress the tendency of polyps to bleed, even to cause serious anemia. In our case, blood was never demonstrated in the feces despite frequent and careful examination. This is an unusual finding with polyposis, particularly since the patient had stools of a diarrhoeic or semi-diarrhoeic character which evidences irritability of

the intestinal tract and hypermotility which one would expect to produce bleeding of the polyps.

One other condition of the intestines which may produce a picture very similar to polyposis though very different in pathology is gastro-intestinal pseudoleukemia. Reproduced herewith is a picture of this condition taken from Ewing's *Neoplastic Diseases* which appears to be a perfect counterpart to the condition observed in the X-rays of the case presented. The pathological changes in gastro-intestinal pseudoleukemia consist of swelling of the lymphoid tissue in different parts of the body, but the characteristic leukemic changes in the blood are absent. Other forms of pseudoleukemia show relative lymphocytosis in the blood, the condition which is mainly localized in the intestines fails to produce this feature. To quote from Ewing, "... the process may be limited to a portion or involve the whole of the gastro-intestinal tract, or it may be associated with widespread lesions of most other lymphoid structure."

Stoerk (7), in 1904, described a case which belongs to this group. The whole intestinal canal showed numerous lesions which consisted of round cell infiltrations. These lesions were partly arranged along the folds of the intestines forming big, oblong masses; in other parts they showed up as a swelling of the Peyer plaques, thus recalling the picture predominant in typhoid. In the discussion of his case Stoerk made a diagnosis of pseudoleukemia by elimination: lymphosarcoma would start from one group of lymph nodes



Fig. 3. Detail film showing polypoid structure in diverticula.



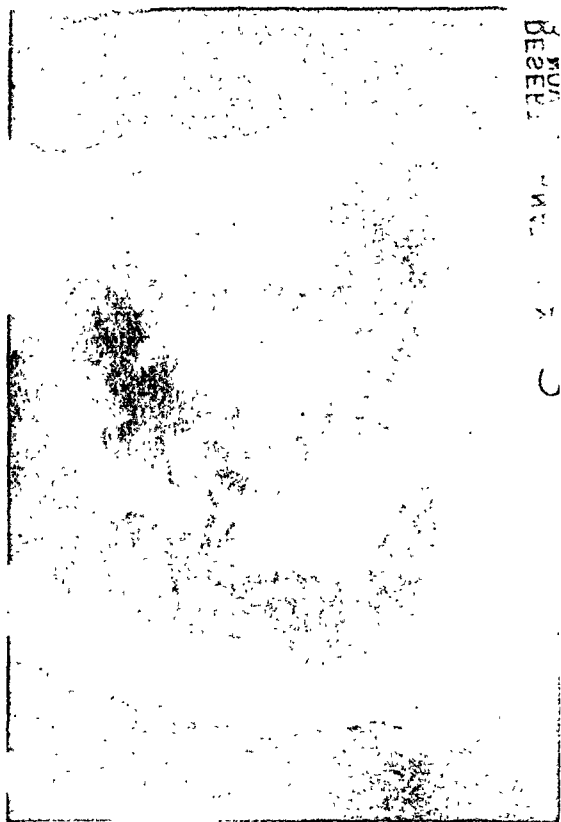


Fig. 4. Roentgenogram of small intestine three hours after ingestion of barium sulphate meal.

and progress from region to region; whereas, in his case the lesions in the intestines were of equal size, therefore, probably of equal age. Absence of metastasis also opposed a diagnosis of sarcomatosis.

Summers (8) reviewed the literature and tabulated the findings in gastro-intestinal pseudoleukemia and reported an additional case observed by himself. The clinical features in his case were similar to the case here reported insofar as his patient showed constantly diarrhoeic stools. However, in his report Summers recorded the stools watery and no mention is made of a conspicuous fat content. The patient showed painlessly swollen lymph nodes at both sides of the neck, and anemia of the hypochromic type; in the differential blood count there was a prevalence of polymorphonuclear leucocytes. The patient died of peritonitis. Autopsy showed enlarged liver and spleen due to swelling of the lymphoid apparatus. The main finding was the presence of myriads of small and large nodes in the intestinal tract, most of them with broad bases, others pedunculated. Those nodes, to quote from Summers, "... were arranged in such proximity to one another that the intervening mucous membrane was scarcely visible." Microscopically the intestines showed the presence of enormous lymphoid collections occupying mucosa and submucosa, replacing and almost completely destroying the glandular elements.

The case reported by Biggs and Elliott (9) showed similar clinical features to the case herewith pre-

sented. No abnormal roentgen findings in the intestine were observed by Biggs and Elliott though at autopsy the findings observed correspond exactly with what one would expect to find from the roentgenological findings we observed in our patient.

In none of the reports of cases of intestinal pseudoleukemia is there shown or described roentgenological findings of the intestinal tract. Lahm (10) reported a case of lymphogranulomatosis of the jejunum in which the loops of the intestine were rigid and the folds were broad and thick but the polypoid structure demonstrated in our case was missing.

The unusual roentgenological findings here presented appear to demonstrate the pathological process which has been described as gastro-intestinal pseudoleukemia. In addition to this roentgenological picture the patient presented clinical findings which have been found in such cases reported by other observers. The distribution of the lesions, the massiveness of the stools, the differential blood count with prevalence of polymorphonuclears are consistent with a pseudoleukemia syndrome. He did not show enlargement of superficial lymph nodes which in most other cases were reported as enlarged. There is, however, the possibility that the considerable enlargement of the liver is due to lymphocytic infiltration.

From the clinical laboratory standpoint the patient presented other interesting features. In the differential blood count the most conspicuous fact besides the polymorphonuclears was the marked shift to the



Fig. 5. Colon roentgenogram following barium enema and evacuation.

left of the nuclear index accompanied by an increased erythrocyte sedimentation rate, indicating unceasing activity of the process. Active disease of the liver with impairment of its function is shown by the constant increase in urobilinogen output in the urine, the reduction in cholesterol esters, the impairment in galactose tolerance, reduced albumin-globulin ratio, and increase in plasma fibrinogen. Noteworthy is the low blood calcium of 7. mgm. %. This feature may be explained by the diarrhea which apparently drained the body of increased amounts of calcium and the fat indigestion which prevented calcium absorption. In sprue a similar finding is observed, in extreme cases causing osteoporosis or even constant tetany as observed in the case reported by Gerdaldy in 1932. There is a

certain resemblance to sprue in the extreme thinness of the walls of the colon.

We are aware that it is impossible to make a sure diagnosis from the observed findings. We believe that, everything considered, the case shows features which fit the picture of pseudoleukemia better than that of generalized intestinal polyposis.

### SUMMARY

Report of a case showing the clinical picture of constant massive fatty diarrhea together with anemia, emaciation, and weakness. The X-ray demonstrated the presence throughout the intestinal tract of innumerable small nodules, suggesting either polyposis or more probably gastro-intestinal pseudoleukemia.

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## Editorials

### A SUBSTANCE IN THE URINE WHICH INHIBITS GASTRIC SECRETION

FOR a period of years investigations in our laboratory have been concerned with a study of enterogastrone, a hormone which is responsible for the inhibition of gastric secretion and motility which follows upon the ingestion of fat (1). Active concentrates containing this inhibitory principle have been prepared from duodenal mucosa (2). These concentrates have not as yet been purified to the point where they are suitable for human administration. They are still contaminated by sufficient protein-like material to cause the development of refractoriness when they are injected for some time into dogs (3).

The observation of Sandweiss, Saltstein and Farbman (4) that commercial extracts of pregnancy urine prevent the development of jejunal ulcers in dogs subjected to the Mann-Williamson operation suggested to Culmer, Atkinson and Ivy (5) that such extracts might contain a substance capable of inhibiting gastric secretion. Accordingly they administered these extracts to dogs with Pavlov pouches and observed a significant and prompt decrease in the secretory response to a meal. Later, Sandweiss, Saltstein and Farbman (6) reported that extracts prepared from normal female urine were also effective in preventing the development of experimental ulcers. A sample of such an extract submitted to us by Dr. Sandweiss proved to be capable of inhibiting gastric secretion.

It occurred to Gray, Wiczorowski and Ivy (7) that this inhibitory principle might be present in all normal urine and that it might represent excreted enterogastrone. Accordingly, extracts of normal male urine were prepared and assayed in dogs with gastric pouches which were secreting in response to a subcu-

taneous injection of histamine. These preparations were found to be highly potent in inhibiting gastric secretion. They were resistant to boiling for five minutes, and they contained little or no gonadotropic activity. In contrast to enterogastrone prepared from duodenal mucosa the urine extracts exerted very little effect on gastric motility. We are not sure that the latter fact constitutes an objection to the hypothesis that the substance obtained from urine is enterogastrone.

At the present time the evidence indicates that the ulcer-preventing principle is distinct from the gonadotropic hormone of pregnancy urine. Furthermore, the ulcer preventive factor now appears to be separate from the inhibitory factor. There are two reasons for this view: First, the doses administered to the Mann-Williamson dogs are too small to exert any easily demonstrable effect on gastric secretion. Second, extracts prepared from the urine of patients with peptic ulcer have been reported by Sandweiss et al (6) to be lacking in the ulcer preventing factor, and by Friedman et al (8) to contain the usual amounts of the inhibitory principle. Whether the inhibitory principle is or is not enterogastrone cannot be stated as yet. The chemical and biological behaviors of the urinary and duodenal extracts are similar, but this evidence is scarcely more than indicative. We are at present carrying out experiments designed to reveal the origin and nature of the gastric inhibitory factor of urine.

"Urogastrone, the substance in urine which inhibits the gastric secretory response to histamine, apparently is formed in the intestine and is related to enterogastrone. This is based on the observation that the substance is present in the urine of fasted dogs but is

not present in the urine of the same dogs when fasted after gastro-enterectomy."

A. C. Ivy.

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## THE USE OF URINE EXTRACTS IN THE TREATMENT OF ULCER

RECENT reports in the literature on the effect of urine extracts on Mann-Williamson ulcers and gastric secretion in dogs have focused attention on the possible therapeutic use of urine extracts in human peptic ulcer. It has been shown that extracts of urine from pregnant as well as non-pregnant women tend to prevent and heal ulcers produced by the Mann-Williamson operation and to prolong the life of the dog (1, 2). It has also been demonstrated that urine extracts have an inhibitory effect on gastric secretion in the dog (2, 3, 4, 5).

Several questions naturally arise: (1) Is the beneficial effect of urine extract on Mann-Williamson ulcers due to the depression of gastric secretion? (2) What effect, if any, has the urine extract on human gastric secretion? and (3) What effect, if any, has the urine extract on the symptoms and course of peptic ulcer in man?

Data obtained so far suggest that the beneficial effect obtained with urine extracts on experimental ulcers in dogs is not due to the inhibitory effect on gastric secretion, but rather to some other factor. These facts are:

(a) The beneficial effect on Mann-Williamson ulcers was obtained with daily subcutaneous injections of the extract in doses too small to be effective in depressing gastric secretion (2, 3).

(b) Extracts from urine of normal (non-pregnant) women tend to prevent the formation of or to heal Mann-Williamson's ulcers, while extracts from urine of patients with peptic ulcer do not have this beneficial effect (2). Both of these extracts, however, when given intravenously inhibit gastric secretion (5). If the substance that depresses gastric secretion were responsible for the beneficial effect on the experimental ulcers, the extract from the urine of ulcer patients (which also possesses the depressor substance) should have produced a similar beneficial effect on the Mann-Williamson ulcers.

Pregnant urine extract (Antuitrin-S) has no effect on human gastric secretion when administered subcutaneously or intramuscularly in daily doses up to 4 cc. (6, 2). Preliminary observations indicate that the same results are obtained when normal female urine extract\* is administered intramuscularly to patients. When it was administered intravenously to two men, inhibition of free acid secretion was obtained in one, while no change was noted in the other. Because these men developed uncomfortable reactions shortly after receiving the intravenous injections, this mode of administration was discontinued.

Twenty patients with peptic ulcer have been treated

by us with an extract\* of urine from normal women. The immediate results are encouraging, but an accurate clinical valuation of the treatment cannot be made until a larger series of patients have been treated and a much larger follow-up period has elapsed. The immediate and remote clinical results will have to be compared with those obtained in a control series (7).

Patients with ulcer who have become symptom-free during intramuscular injections of the urine extract have not shown a definite reduction in gastric acidity either during or following treatment.

\*Prepared for us by Parke Davis & Company.

David J. Sandweiss and M. H. F. Friedman.

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## EFFORTS TO FIND A NEW, GOOD AND SAFE MORPHINE-LIKE DRUG

AN article which will be of interest to many readers of this Journal is that of Nathan B. Eddy in the April, 1939, number of the American Journal of the Medical Sciences. It constitutes a progress report of work that has been carried out during the past ten years under the auspices of the Drug Addiction Committee of the National Research Council, by pharmacologists at the Universities of Virginia and Michigan. Some twenty-seven chemists have been kept employed at this work. They have been trying to find an analgesic which will replace morphine and do its work without producing addiction. Obviously, there were two lines open along which they could work; first, they could try to so rearrange or modify the morphine molecule as to remove undesirable by-effects, or second, they could start from scratch with some new nucleus and build onto that until they found what they wanted.

Working along the first line, a methyldihydromorphinone was produced, which is promising. In man it is twice as effective as an analgesic as is morphine. It has shown no emetic effect and no sign of depression of respiration. It seems to have little tendency to produce habituation. Work is still being done on it.

Experimenting along the second line the pharmacologists have made drugs built up upon the phenanthrene nucleus which is characteristic of morphine. The most effective analgesic of this type synthesized so far is one derived from tetrahydrophenanthrene with a hydroxyl radical attached to the nucleus, together with a tetrahydro-isoquinoline group. The drug is definitely analgesic and depressant but so far hasn't

shown other typical morphine attributes. Experimental work is now being done with this new drug.

W. C. A.

### THE VALUE OF GASTROSCOPY TODAY

THERE can be no question now that gastroscopy is a most helpful technic and one that must be used every so often by the gastro-enterologist. Questions that still need to be answered by experience are: In what cases should the gastroscopist be called in; how often can he find a lesion when the roentgenologist has failed to do so, and what connection has the gastritis, which is so commonly found, with the symptoms complained of.

It would seem obvious that in all but a few cases the roentgenologic technic should be used first, because it is so simple and so without discomfort for the patient. In those many cases in which it appears to have settled the matter of the diagnosis, there would seem to be little reason for looking directly into the stomach. Certainly few of us physicians would permit a gastroscopist to be passed on us or on a loved one after a duodenal ulcer or a gastric carcinoma had been clearly demonstrated. Similarly, few physicians, especially under the age of thirty-five years, would want to be gastroscopied if, with a history of much nervousness and overwork and symptoms strongly suggestive of a functional disturbance, the roentgenologic examination of the stomach and duodenum had shown perfect outlines.

Where the gastroscopist can help most is in those cases in which, after the roentgenologic examination has failed to reveal a lesion, the clinician still feels that there must be some organic cause for the symptoms. They may be severe, or they may be coming out of a clear sky in a person who is not of a frail, nervous, or complaining type. One wants also to look into the stomach when the patient has been bleeding without discoverable cause, or when, especially in an older man or woman, there are roentgenologic signs of some lesion in the stomach, such as an ulcer, a tumor, or a hypertrophic gastritis. Surely there can no longer be any excuse for the physician who lets a patient drift on into an inoperable condition with carcinoma of the stomach, and now that the diagnosis of this disease can be made as soon as symptoms appear the mortality should be much lowered.

Light on this subject was thrown recently by E. Bulmer who reported in the "British Medical Journal"

for July 15, 1939, that in 38 per cent of 1575 "gastro-duodenal cases" only an indefinite diagnosis could be made by the clinicians. Of the 589 patients with such an indefinite diagnosis, 147, all with negative roentgenologic findings, were sent for gastroscopy. In sixty-six cases nothing abnormal was found. In another sixty a diagnosis was made of chronic gastritis. Gastric ulcer was found in eight cases. In one case an ulcer was found and later this was shown to be malignant. One curious lesion was found which later proved to be an ulcer, and one inoperable carcinoma was found.

Bulmer seems to have felt it incumbent upon the gastroscopist to find disease in every one of the stomachs examined, but obviously this is not necessary. One of the curious relics of a time when the stomach was looked on as the organ of digestion is the tendency on the part of most physicians and even physiologists to think and talk only of the stomach, and to study only its functions in health and disease.

Actually, as everyone would admit after a moment's thought, the small bowel is the essential organ of digestion and absorption, and surely one must expect a few of the disturbances of digestion to arise in malfunctions of this long muscular tube. Incidentally, this being true, is it not a most curious and disgraceful fact that we gastro-enterologists rarely study the small bowel with the roentgen ray, and we practically never test its all-important functions of digestion and absorption. We can get but a faint idea of the appearance or state of health of the mucous membrane, and when, on rare occasions, we do note with the roentgen ray that this part of the digestive tube empties too fast or too slowly, we can make only the vaguest guesses as to why it is working so poorly. One of the greatest advances in gastro-enterology will come when someone shows us how to inquire into the condition and the several functions of the small bowel. Until this can be done we physicians must expect to see many cases of indigestion, abdominal discomfort, or diarrhea in which we cannot make a definite diagnosis.

In the meantime, when the gastroscopist does demonstrate gastritis we had probably better not jump always to the conclusion that it explains the symptoms complained of. We have every reason to believe that gastritis must often be symptomless, just as peptic ulcer and cholecystitis are often symptomless, for long periods of time.

W. C. A.

## Book Reviews

*The Genetics of Schizophrenia. A Study of Heredity and Reproduction in the Families of 1,087 Schizophrenics.* By Franz J. Kallmann. New York, J. J. Augustin, 291 pp., 1938.

EVERY gastro-enterologist has to be somewhat of a psychiatrist if he is going to be worth his salt. Few probably realize that according to several sets of careful investigators, one person out of every nineteen born in this country is going to be committed some day to an asylum for either the insane, the feeble-minded, or the epileptic! Since about half of the

mentally deranged persons are going to have schizophrenia, one can gain some idea of the importance to the nation and to physicians of this disease.

Worse yet, as Alvarez has pointed out, every insane person has a group of relatives, a considerable number of whom suffer with peculiar and often disabling nervous disorders. Many of them have puzzling abdominal discomforts and pains, many are weak and tired and complaining all their days, and most of them go to gastro-enterologists in search of help. Unfortunately the average physician has so little training in

psychiatry that usually it does not occur to him that the main basic trouble with the frail little woman who sits before him, telling him about many fruitless operations, is that she is almost insane. Actually many physicians today refuse to believe that the apparently sensible patient before them is insane, after a psychiatrist has apprised them of the fact.

In this book on the genetics of schizophrenia, Dr. Kallmann reports the results of a tremendous amount of work which appears to have been done scientifically and honestly and with care to avoid mistakes. The study was made in Germany where it probably is much easier to find the relatives of patients than it would be here in America. Most important is the fact that Dr. Kallmann and his associates interviewed personally the relatives of the 1,087 insane patients studied. As anyone knows who has ever tried to make patients confess as to their insane ancestry, a questionnaire would bring forth very little of the desired information.

Altogether, Kallmann and his associates studied over 3,000 parents and grandparents, over 3,000 direct descendants, nearly 4,000 brothers, sisters, half-brothers and half-sisters, and over 2,000 nephews and nieces. The data show that 16.4 per cent of the children, 11.5 per cent of the brothers and sisters, 3.9 per cent of the nephews and nieces, and 4.3 per cent of the grandchildren of persons with schizophrenia went insane. The disease is apparently inherited as a recessive character but probably not as a unit character. Another important point is that, as one would expect, the taint is inherited in many different forms. Many of the relatives were psychopathic, feeble-minded, or alcoholic, and many were troubled with psychoses.

A striking fact that came out of this study, as well as out of other previous studies of schizophrenics, is that there is a close correlation between the inheritance of the psychosis and the incidence of tuberculosis in the defective families. This tendency serves to a slight extent to wipe out the bad stock. Another factor that helps somewhat to obliterate the stock is the failure of many of these psychopathic persons to marry or to rear many children.

It is obvious from these studies that the sterilization of the insane patient alone will not help much in wiping out the defective stock or in controlling the disease. And yet civilization must eventually try to protect itself somehow. We cannot vouch for the fact, but we were told recently by a man who should know, that in his state more money is being spent each year for the care of the insane and the feeble-minded than is spent on the education of boys and girls who have a good brain!

In answer to those persons who maintain that a schizophrenic goes insane simply because of psychic traumas, Dr. Kallmann describes cases like the following: Two girls, identical twins, were separated at birth. One of them was brought up in a poor home, and at fifteen went into a factory, where she was promptly seduced. Following the mental trauma of bringing into the world an illegitimate child, she went insane. There we have a common type of history, but unfortunately for the argument of those who maintain that the psychic trauma was all that was necessary to upset the girl's mind, the other sister, who was brought up in a good home and had an easy and happy

life, also went insane and joined her twin in the asylum!

*Attaining Womanhood.* By George W. Corner. New York, Harper & Brothers, 95 pp., 1939. Price \$1.00.

SO many people were pleased with Dr. Corner's little book on "Attaining manhood" that he has now written a similar book for girls. Anyone who knows Dr. Corner and his interests would expect him to prepare as he has done, a fine dignified discussion, mainly of the anatomy of the pelvic organs and the physiology of reproduction. There are some small chapters on sexual attraction and sexual conduct, the sex problems of girlhood, and venereal diseases.

It is hard to know how far one should go in the instruction of children of different ages in regard to sex. We have the feeling that this book is a little more technical than it need be. We have the feeling also that a little later, when girls reach the ages of perhaps seventeen or eighteen, when the sex urge becomes stronger, temptations greater, and real problems come clamoring for solution, a girl will need definite information about intercourse and especially the psychic and other problems and dangers which come when illicit relations are entered into.

There is great need then for a frank, dispassionate and unreligious discussion of all the problems involved. It would seem well to admit the desirability of having a sex life, but at the same time to tell about the dangers of attempting to have an illicit one. The problems of the long engagement and of those many young people who want to marry but can't afford to do so should be discussed frankly and with much sympathy. A book like Dr. Hotep's "Love and Happiness" will then be a good one for the girl to read.

The trouble with many of the books on sex is that they describe the anatomy and physiology of reproduction but leave out a discussion of those all-important psychologic reactions which, if satisfactory, make for a happy marriage or liaison, and which, if unsatisfactory, bring unhappiness and feelings of guilt and disgust. Many women and men need some information also in regard to the psychopathic types of reaction, as in cases of homosexuality.

*Diagnosis and Management of Diseases of the Biliary Tract.* By R. F. Carter, C. H. Greene and J. R. Twiss. Philadelphia, Lea & Febiger, 432 pp., 1939. Price \$6.50.

GASTRO-ENTEROLOGISTS will find this a helpful volume. As the authors say, "the principal purpose of this book is to present a brief treatise on present-day concepts of the basic factors in gall bladder disease and an outline of those methods of investigation which will provide for a division of patients into those who are to be treated surgically and those who are to be treated medically. The basic factors upon which these recommendations are made have been derived from the follow-up findings on patients who were subjected to a division and management which is here outlined."

There is a short appendix by Drs. Heyd and Hotz on the results of operative work. Chapter 28 by Dr. Maraffino is on cholangiography. There is a chapter on carcinoma of the pancreas by Drs. Russell and Hinton. Chapter 22 is on the dyskinesia, a subject

which has recently excited much interest.

The book is well illustrated, well printed, and well documented.

*The Digestive Tract: A Radiological Study of Its Anatomy, Physiology and Pathology.* By Alfred E. Barclay, London, Cambridge University Press, 395 pp., 1933.

It may be a little late to review Barclay's book, but we just had occasion to consult it again, and felt that it would do no harm to call the attention of gastro-enterologists to an excellent book which they may not know as well as they should. Barclay has always been one of the world's leaders in roentgenology. For years he has worked in roentgenology purely for the fun of it and from the point of view of a research man. After years spent in a busy practice he gave up his practice and took a lectureship in roentgenology at Cambridge. There he gathered about him a group of enthusiastic students and did a lot of interesting research. He is now at The Nuffield Institute for Medical Research at Oxford.

Several years ago he gathered the results of many years of study and observation into the book now before us. It is an excellent book, well written and beautifully printed and illustrated, and there is much in it that a gastro-enterologist should know well. There is much to make the reader think. One of the many fine things about this book is that Barclay is interested not only in describing diseases but in trying to find out in what way the normal physiologic activity of the body has become deranged.

## Abstracts

INGRAHAM, R. C. AND VISSCHER, M. B.

*Analyses of Gastric Mucosa and Pancreatic Gland Tissue of Dog for H<sub>2</sub>O, Na, K, Cl and PO<sub>4</sub>.* *Proc. Soc. Exp. Biol. Med.*, 40(2):147-149, 1939.

Analyses of pancreas and gastric mucosa show relatively more Na and Cl in the latter than the former; and the reverse for K. The PO<sub>4</sub> contents are not significantly different. Gastric mucosa contains consistently more water. The results are discussed in relation to secretory function.—Authors (Courtesy of Biol. Abst.).

CROHN, BURRILL B. AND YARNIS, HARRY.

*The Anatomical Position of the Ileum in Health and Disease.* *Radiology*, Vol. 33, No. 3, p. 325-330, Sept., 1939.

In healthy persons the position of the terminal ileum depends upon the position of the cecum; which latter

again depends to a certain extent, upon the existence or non-existence of the mesentery of the ascending colon. If the ascending colon is fully peritonealized with an ample mesentery, which occurs in 26% of cases, the cecum is likely to hang low in the iliac fossa or over the brim of the pelvis. If it possesses no mesentery, it will likely be found fixed and firm in the iliac fossa above the brim of the true pelvis. In 90% of the cases, the cecum is fully surrounded by peritoneum; in 10% it is more or less adherent in the false pelvis. In upright or standing position, these loops of the ileum fall into the space between bladder and rectum in the

male, or between the posterior surface of the uterus and the anterior surface of the rectum in the female. Very often these loops lie directly on the lowermost point of the pelvic floor, in the cul-de-sac actually between the posterior wall of the vagina and the rectal surface behind.

In 25 cases of terminal ileitis, the pathological terminal loop lay within the true pelvis; in fact on the floor of the pelvic cavity, its course as in the normal control cases, upward to its entrance at the ileocecal junction. In the diseased instances, the ileocecal junction is regularly at or below the level of the first sacral vertebra (usually fixed by adhesions) and the

.. for Gastro-Intestinal Dysfunction

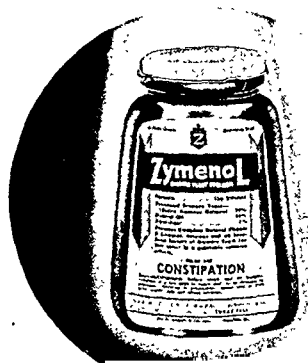
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terminal inches of the ileum descend directly to the pelvic floor.

In 15% of the authors observed clinical cases of ileitis, they noted perineal fistulas as a complicating factor. The authors have reason to believe that a direct fistulous tract made its course from the diseased loop of the ileum lying on the floor of the true pelvis, seeping downward through the fascial planes to make its exit somewhere on the perineum between the rectum and the vagina and involving either one or both of these organs.

Franz J. Lust, New York, N. Y.

ALVAREZ, WALTER C.

*Abdominal Discomforts for Which No Organic Cause Can Be Found. Medical Clinics of North America, Mayo Clinic No., July 1939.*

Alvarez discusses several abdominal conditions which are so common but for which no organic cause can be found. There is a so called "mucous colitis." Alvarez pleads not to use this expression. The colon in this case is not ulcerated or inflamed. There is abnormality in the excretion of an increased amount of mucous. The roentgenological examination reveals a somewhat exaggerated haustration in

the descending colon, with perhaps a fine crinkling of the muscular wall. Alvarez pleads that these signs should not be called to the attention of the patient and should not be called pathological.

Another condition which he calls "pseudo-appendicitis" is just as baffling. The patients describe their discomfort as a burning or a pulling sensation or a gurgling. The roentgenological or anatomical reason could not be found. Even  $\frac{1}{2}$  gr. of morphine is not able to stop the pains. Alvarez thinks that in some of these cases the trouble appears to be due to irritation of spinal nerves involved in that type of inflammation which produces mild spondylitis, or fibrositis, neuritis, and myositis around the spine.

Flatulence, pseudo-ulcer, and pseudocholecystitis are further discussed. Spondylitis is shown to be the main cause of pains. It is very important to know these conditions and to be aware of not having unnecessary surgical procedures applied to these patients.

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KERPPOLA, W.

*Über die klinischen Kennzeichen und das Auftreten des Iktus und seiner verschiedenen Formen. Acta Med. Scand., 98(3):262-279, 1 fig., 1939.*

The author describes the formation of bilirubin, its occurrence in the body and its separation. About 2,000 cases of icterus were examined, and 3 forms of icterus are considered namely: haematogenous or haemolytic jaundice, the hepatogenous polychymatoses or obstructive jaundice and the hepatic congestive or gall stone jaundice. Cases of icterus can fall into one of these classes, or may be looked upon as intermediate transitional forms. The so-called Salvarsan-Icterus is almost always a syphilitic catarrhal jaundice but hepatic syphilis (cirrhosis) is considered to be an uncommon disease.—J. F. Wilkinson (Courtesy of Biol. Abst.).

SCHINDLER, RUDOLF.

*Chronic Gastritis. Bull. New York Academy of Medicine, Vol. 15, 5, 322, May, 1939.*

Schindler describes his experience in chronic, non-specific gastritis. He publishes his gastroscopic views besides the microscopic photos of his cases, which renders his paper especially important.

Schindler distinguishes (1) chronic superficial, (2) chronic atrophic and (3) chronic hypertrophic gastritis. The etiology is unknown. Roentgenologically he found a tenderness of the gastric silhouette. In the super-



ficial inflammation the general symptoms are in the foreground of the clinical picture. These patients are mostly treated as psychoneurosis. The hypertrophic type is also a severe disease. Its symptoms are highly suggestive of a peptic ulcer. The atrophic gastritis should be gastroscopically diagnosed for it is apparently a precancerous condition. The relation between gastric atrophy and pernicious anemia is discussed. Schindler's observation led him to believe that there must be a primary dysfunction of those cells which produce the anti-anemic factor, and a secondary degeneration of the gastric surface epithelium with following genuine inflammation.

Franz J. Lust, New York, N. Y.

HIGGINS, GEORGE M. AND INGLE, DWIGHT J.

*Regeneration of the Liver in Hypophysectomized White Rats.*  
*Anat. Rec.*, 73(1):95-104, 1939.

Hepatic regeneration following partial removal of the liver was studied in 3 groups of white rats: (1) Normal rats which were fed adequate amounts of food. (2) Rats which were fed restricted amounts of food daily. (3) Rats from which the pituitary gland was removed 1 week prior to partial hepatectomy. 5 animals in each group were sacrificed at 24 hours, 48 hours, 72 hours, 1 week and 2 weeks, following removal of the liver. The regenerating livers were quickly removed and weighed. Regeneration of the liver occurred in the hypophysectomized animals but to a far less extent than in normal animals. Regeneration of the liver occurred in animals fed restricted amounts of food daily, but likewise to a far less extent than in normals. Greater amounts of liver regenerated in animals fed the restricted amounts of food than regenerated in the hypophysectomized animals which consumed about the same amount of food daily. Regeneration of the liver seems to depend largely upon the amount of food consumed; but on the basis of total average weights of liver which regenerated in the three groups of animals, it is possible that the loss of the pituitary gland may have had some inhibitory effect upon the extent of regeneration. — Author (courtesy of Biological Abstracts).

GOLDEN, ROSS.

*The Small Intestine and Diarrhea.* Dept. of Radiology of the Presbyterian Hospital, Vol. 36, No. 6, p. 892-901.

The importance of the examination of the small intestine in diarrhea is considered by Golden. Diarrhea is a symptom which is not always due to

a disease of the large intestine. The most important cases of diarrhea due to pathology in the small intestine are nonspecific granuloma. The lower part of the ileum is more frequently involved than any other portion of the intestinal tract. In nonspecific granuloma of the small intestine psychic disturbances are very often thought to be responsible until roentgen studies disclose the evidence of the disease of the small intestine. Any kind of neoplasm can cause diarrhea also. In deficiency diseases a flocculation of the barium in the ileum, the tendency to form small rounded or oval flecks of barium in-

stead of the smoothly homogeneous continuity of the barium shadow as seen under normal conditions. The possibility that abnormal fat digestion with abnormal quantities of fat, fatty acids or soaps, or some other abnormal non-opaque material in the intestine might be responsible for this is suggested.

In nervous diarrhea the small intestine study disclosed unusual hypermotility of the jejunum and ileum. In one case the barium reached the cecum in 45 minutes and the ileum was empty in 3½ hours. The large intestine showed no evidence of irritability. It is interesting that besides

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the irritability of the small intestine no other signs of a neurosis could be found.

Franz J. Lust, New York, N. Y.

EUSTERMAN, GEORGE B.

*Chronic Gastritis. The Medical Clinics of North America, Vol. 23, No. 4, p. 847-859, July, 1939.*

Eusterman discusses chronic gastritis. The difficulty of evaluating the microscopic findings had a retarding influence on the reactions of this condition. Every adult would have chronic gastritis if we regarded as abnormal any anatomic alternation of

the gastric mucous membrane such as interstitial cellular infiltration which, in addition to other phenomena, Roesle considered to be within physiologic limits. If we accept such a minimal yardstick, apparently unwittingly proposed by the pathologist, the clinical significance of gastritis as an entity disappears.

The cause of a more thorough recognition of gastritis is due to the more general use of the gastroscope, the possibility of anatomical studies of resected parts of the stomach, and the development of an improved roentgenologic technic, so-called compression technique, which permits

battery visualization of the mucosal relief. Gastroscoy is the most important means for examination, roentgenological examination is only of value in the hypertrophic forms of gastritis. Eusterman suggests as treatment a smooth diet, an adequate intake of vitamins, liver extract, weak alkaline solutions, as well as stomach lavages.

Franz J. Lust, New York, N. Y.

SECKEL, H. P. G.

*The Influence of Various Physiological Substances on the Glycogenolysis of Surviving Rat Liver. The Influence of Insulin Added in Vitro. Endocrinology, 23(6): 760-766, 2 figs., 1938.*

Rat liver glycogenolysis as it normally occurs in surviving tissue slices suspended in a buffered salt solution was shown to be inhibited to a considerable extent by large doses of insulin added to vitro (up to 43 at 4 U. per cc.). Because of this finding and results reported in literature, the essential action of insulin on the liver is believed to be an inhibition of the glycogenolytic process, particularly when the latter is proceeding at a high rate.—D. Permar (Courtesy of Biol. Abst.).

BUNDE, CARL A. AND HELLBAUM, ARTHUR A.

*Some Chemical and Physiological Properties of the Gonadotropic Antagonist. Am. J. Physiol., 125 (2):290-295, 1939.*

The pituitary antagonist inhibits the action of concurrent injections of gonadotropic hormone. It is present in crude gonadotropic extracts, and upon fractionation it is found with the luteinizer. Subjecting sheep ant. pituitary preparations to a high pH destroys the antagonist as well as the gonadotropic principles but extended boiling and a low pH destroys all gonadotropic activity without affecting the antagonist. The possibility of other known ant.-lobe hormones withstanding this treatment is discussed.—Authors (Courtesy of Biol. Abst.).

HERFORD, K.

*L'influence de la Vitamine A sur la Secretion Externe du Pancreas. Acta Med. Scand., 96 (5/6):425-437, 2 figs., 1938.*

Pancreatic juice was collected by duodenal intubation; total vol., lipase, and trypsin were estimated. Vitamin A by mouth or intramuscular stimulated pancreatic secretion even after intravenous injection of secretion. In hypochlorhydric patients, Vitamin A caused considerable subjective and objective improvement, without increasing acid secretion.—M. C. G. (courtesy of Biological Abstracts).

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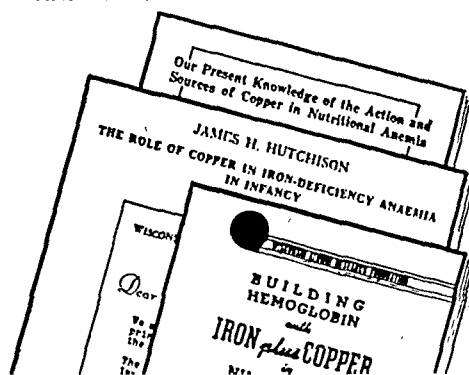
\*"In nutritional and secondary anemia iron and copper in combination was more effective than iron alone<sup>1</sup>. ¶ Iron is best utilized in the presence of copper, which is necessary for haemoglobin synthesis<sup>2</sup>. ¶ Nearly all workers agree that copper is an active agent in haemoglobin synthesis<sup>3</sup>. ¶ Where other means of treatment have failed, copper will prove to be a valuable adjunct<sup>4</sup>. ¶ The effect of the copper was to increase the proportion of retained iron found as haemoglobin<sup>5</sup>. ¶ The presence of copper is necessary for the utilization of this stored iron (in liver) in the production of haemoglobin<sup>6</sup>. ¶ The average haemoglobin values were 15% higher (Iron and Copper) than controls (iron alone)<sup>7</sup>. ¶ 'Iron alone usually stimulates a slight increase in the formation of haemoglobin ... but the response is inadequate. Iron supplemented with copper causes a maximum response in the regeneration of haemoglobin'<sup>8</sup>. ¶ Its (copper) chief value to human health is its effect on the availability of iron as a cure of anemia'<sup>9</sup>".

### REFERENCES—

- (1) Lewis: J.A.M.A., 96:1135, April 4, 1931. (2) Caldwell and Dennett: Med. J. and Rec., March, 1932. (3) Editorial, J.A.M.A., Dec. 17, 1932. (4) Dwyer: J. Mich. St. Med. Soc., Vol. 29, No. 2, June, 1930. (5) Josephs: J. Biol. Chem., XCVI, 558, 1932. (6) Howell: Text-book of Physiology, 13th Ed., p. 1013. (7) Usher, MacDermot and Lozinski: Am. J. Dis. Child., 49:642, March, 1935. (8) Elvehjem, Duckles and Mendenhall: Am. J. Dis. Child., 53:785, March, 1937. (9) Seifriz: Protoplasm (McGraw Hill) 1st Ed., pp. 435, 519.

\*Quoted from Christian P. Segard, M.D.,  
*Am. J. Digest. Dis.*, July, 1939, pp. 315-318.

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SCHOENE, HANS.

*Die galletreibende Wirkung von Derivaten des p-Tolylmethylcarbinols und der Ferulasäure. Arch. Exp. Path. u. Pharmacol., 190:372-375, 1938.*

Robbers (ibid., 181:328, 1936) has shown that the substance present in *Curcuma domestica* which exerts a bile secretion enhancing action is p-tolylmethylcarbinol, while the dyestuff fraction acts to contract the gall bladder rather than to increase secretion of bile. Para-tolylmethylcarbinol being insoluble in water, the Na salt of a camphoric acid ester

thereof (A), also its orthophthalic acid ester (B), were studied. Since the dyestuff in curcumin is diferuloylmethane, the effects of ferulic acid (C) and of hydroferulic acid (D) were also studied. Intraven. administered (A) and (B) increased bile secretion in guinea pigs (A more effectively than B). Na ferulate, intraven. given, was irregular in effect. The hydroferulate produced more bile secretory effect than the ferulate, but both appeared to act chiefly by contracting the gall bladder. Effects of (A) and (B) were confirmed in dogs. (C) and (D) slightly increased bile secretion in the dog,

but chiefly increased contraction of the gall bladder, even to the extent of 2000 per cent over normal.—C. S. L. (courtesy of Biological Abstracts).

ZOLLINGER, ROBERT AND KEVORKIAN, ALBERT Y.

*Surgical Aspects of Obstructive Jaundice. The New Eng. J. of Med., Vol. 221, pp. 486-488, Sept. 28, 1939.*

In a correlated study of seventy-five cases of common-duct stone and forty-nine consecutive cases of carcinoma of the head of the pancreas, the authors believe that there is sufficient contrast in symptoms to make a differential diagnosis between these causes of surgical obstructive jaundice without the use of laboratory procedures. A table comparing the symptoms and findings in these cases is extremely interesting and self explanatory.

Symptom or Finding	Diagnosis	
	Common-Duct Stone %	Carcinoma of the Head of the Pancreas %
Past history suggesting		
gall bladder disease	100	18
Colic	91	16
Location of Pain		
Right upper quadrant	53	20
Epigastrium	40	33
Left upper quadrant	5	2
Referred to back	67	18
Weight loss	25	86
Jaundice:		
Incidence	81	88
Intermittent	35	12
Vomiting	77	37
Chills	33	8
Sex:		
Male	13	69
Female	87	31
Enlarged gall bladder	12	55
Enlarged liver	25	80
Operative mortality	10	31
Age in years (average)	55	58

In treating patients with pancreatic malignancy, the authors have devised a valvular type of cholecystgastrotomy which forestalls ascending biliary infection. This procedure is only to be considered as a preliminary step to resecting the neoplasm.

Henry H. Lerner, Boston.

ERWTEMAN, J. AND HEERES, P. A.

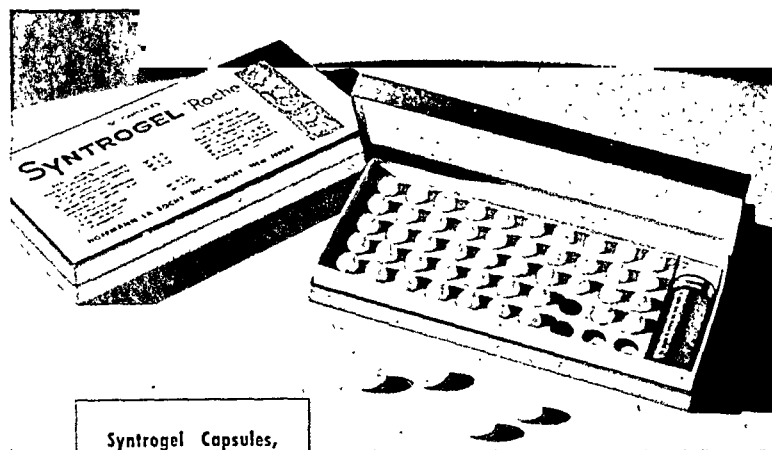
*Clinical and Experimental Observations About Alcohol-Tolerance. Acta Med. Scand., 96(2/4):199-216, 22 figs., 1938.*

The alcohol tolerance test can be used to determine impairment of hepatic function in liver diseases, and characteristic curves are obtained; examples are given. Similar tests were used in heart and lung diseases.—J. F. W. (courtesy of Biological Abstracts).

HESSER, S.

*On Relapsing Gastric Hemorrhages and Their Treatment. Acta Med. Scand., 98(4/5):340-354, 2 figs., 1939.*

122 cases of relapsing gastric hemorrhage were examined; 30% were due to gastric ulcers. One re-



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\*"PEPTIC ULCER—The Effect of High Protein Diet on the Behavior of the Disease" by Windwer and Matzner, Am. Jl. Dig. Dis. 5:743, 1939.

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lapse occurred in 57% but two or more relapses were quite common. They occurred mainly between 30-60 years of age, and were more than twice as common in males as in females. Duodenal ulcers predominated (double) over gastric ulcers. Prognosis in this series showed 3.3% mortality in 122 cases, 3.9% mortality for primary hemorrhages, but only 1.7% of the total number of hemorrhages. 30 cases had recurrent hemorrhages since gastric operation. The results suggested only secondary importance should be attached to a previous hemorrhage as indication for gastric operative measures.—J. P. Wilkinson (Courtesy of Biol. Abst.).

DRIPS, DELLA G. AND OSTERBERG, ARNOLD E.

*An Evaluation of the Frank Method for the Determination of Prolan (Gonadotrophic Principle) in the Urine of Nonpregnant Women. Endocrinology, 29(6): 703-710, 3 figs., 1938.*

292 detns. were made on the urine of 248 females. Of these 235 presented a clinical picture which suggested abnormal gonadotrophic function of the ant. lobe. 13 apparently normal females were used as controls. The clinical diagnosis in each case was made before the prolan detn. was reported. The amount of prolan

found in the urine helped to substantiate the diagnosis. Immature mice were used, and the uteri and ovaries weighed and the ovaries sectioned and stained. Instead of 60 cc. of urine, 400 cc. was used, and in the final amount for biologic assay 2 cc. represented 100 cc. urine.—D. Permar (Courtesy of Biol. Abst.).

HAMBURGER, CHRISTIAN.

*The Assay of Gonadotrophic Hormones. III. Comparison Between Rat and Rabbit Dose-Response Curves for Crude and Purified Preparations of Human Pregnancy Urine and Mare Serum Hormone. Quart. J. Pharm. and Pharmacol., 11(4):673-678, 1938.*

A conditio sine qua non of the practical usefulness of standards for gonadotrophic hormones is qualitative constance of the different types. In this work a comparison of the action is made between crude and purified preps. from pregnancy urine and mare serum hormone. The crude tannate from pregnancy urine and a purified prep. gave qualitatively constant results as measured by uterine and ovarian dose-response curves, the luteinising effect on immature rats and the reaction curves for virgin rabbits. One untreated sample of pregnant mare's serum also showed qualitative constancy concerning the reactions in rats and rabbits.—McGuigan (Courtesy of Biol. Abst.).

MACDONALD, A. M. AND ROBSON, J. M.

*The Production of Vaginal Mucification with the Synthetic Oestrogen, Triphenyl Ethylenc. J. Path. and Bact., 48(1):95-98, 1 pl., 1939.*

Previous investigations have shown that the synthetic oestrogen triphenyl ethylene not only produces vaginal keratinisation in the lower rodents but also a series of changes in the dog, rabbit and monkey similar to those produced by the natural oestrogens. The present expts. show that triphenyl ethylene will also produce vaginal mucification similar to that produced by small doses of oestrin and that as in the case of the natural oestrogen the mucification is increased when progesterone or testosterone is given at the same time.—Authors (Courtesy of Biol. Abst.).

MUNICH, JAMES C.

*The Pharmacology and Bio-Essay of Insulin-Free Pancreatic Extracts. Rev. Gastroent., 6(1):50-53, 1939.*

Pancreas is extracted with HCl and alc. at pH 2.4. The extract is neutralized with NH<sub>4</sub>OH and filtered. The filtrate is acidified with H<sub>2</sub>SO<sub>4</sub>, concentrated in vacuo, and fat is re-



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tongue, isolated intestinal and uterine strips of rats, guinea pigs and rabbits and on the blood pressure of anesthetized rabbits, guinea pigs, cats and dogs. Cyanosis is produced in the cock's comb. One unit is defined as the amount required to neutralize the pressor activity of 12 of epinephrine. — G. H. C. (courtesy of Biological Abstracts).

VIEHOEVER, ARNO.

*Evaluation of Cathartics. J. Am. Pharm. Assn., 27(8):668-671, 1938.*

30 standardized 10 day old Daphnia magna, non-gravid with 100 per cent

filled intestine, cultured in 0.1 per cent dried cow or sheep manure medium at 68-72° F. and pH 7.8-8.1, are individually placed in flat test tubes containing 0.5 cc. of the test substance in 1 per cent, 0.2 per cent and 0.01 per cent concentration in culture medium respectively. The speed and extent of evacuation is recorded with suitable magnification. These results are compared to the cathartic action of the standard reference solution (under similar conditions) made up as follows: suspend 0.1 Gm. of elaterin (Merck) in 100 cc. culture medium and filter through coarse paper. Elaterin Bm.p. 197° C. is preferable, using 0.02 Gm. per 100 cc. culture medium.—I. C. (courtesy of Biological Abstracts).

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1. Privitera, A. T. Arch. of Ped., April, 1938.
2. Eddy, Walter E., (Special Research Report on Vi-Syneral).
3. Allen, A. M., Medical Record, April 19, 1939.

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HAMILTON, JOSEPH G.

*The Rates of Absorption of the Radioactive Isotopes of Sodium, Potassium, Chlorine, Bromine, and Iodine in Normal Human Subjects. Am. J. Physiol., 124(3): 667-678, 1938.*

These radioactive elements were prepared by the use of a cyclotron and then made up as isotonic solutions and given by mouth to normal human subjects in the fasting state. The appearance, and rate of increase of the number of radioactive atoms in the subjects hands was measured by a Geiger counter and the values obtained were assumed to represent the rates of absorption. The radioactive atoms of Na, Cl, Br, and I appeared in the hand within 3 to 6 minutes after ingestion and absorption was apparently completed within 3 hours. The radioactive atoms of K took from 6 to 15 minutes to appear in the hand and complete absorption required more than 5 hours.—J. G. H. (courtesy of Biological Abstracts).

JOSEPHSON, B., JUNGNER, G. AND RYDIN, A.

*Elimination of Cholic Acids. I. In Healthy Animals. Acta Med. Scand., 97(3/4):237-253, 1938.*

Cholic acids are absorbed mainly in the liver but also in the walls of blood vessels. After portal injections of bile salts there is a delayed absorption due either to hepatic intoxication from the excessive supply of bile salt or to exhaustion of the excretory power of the liver cells. Delayed secretion after intraportal injection of china ink or thorotrast is not due to reticuloendothelial block. Consequently intraven. rather than oral administration of bile acids in large amounts is preferable for the augmentation of bile flow. Bile acids are excreted in the unconjugated form for the first 30 minutes, but the conjugated form increases thereafter,



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\*Archives of Pediatrics,  
November, 1939.

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suggesting an enzymatic process.—J. F. W. (courtesy of Biological Abstracts).

KOKAS, E. V. AND LUNDANY, G. V.

*Weitere Untersuchungen über die nervöse Beeinflussung der Darmzottenfunktigkeit. Pflügers Arch. Ges. Physiol., 241(2/3):268-271, 1938.*

In dogs chloralose narcosis, weak vagal stimulation produces a moderate increase in the automatic activity of the intestinal villi without any effect upon the tone of the villi and upon the blood flow in their capillaries. Eserine increases and atropine

abolishes this vagal effect. The depressing effect of splanchnic stimulation is more marked on the motor activity of the villi than upon the tone of the villi or upon the capillaries. Cocaine increases and ergotoxin abolishes this splanchnic effect.—E. F. (courtesy of Biological Abstracts).

PETERS, HOWARD C. AND VISSCHER, MAURICE B.

*On the Mechanism of Active Absorption from the Intestine. J. Cell. and Comp. Physiol., 13(1): 51-67, 1939.*

Studies have been made of the movement of deuterium oxide be-

tween intestinal lumen and blood, simultaneously with measurements of the rate of absorption of NaCl against its conc. gradient. Deuterium oxide moved most rapidly when the rate of active chloride absorption was greatest. Calculations of the rates of solvent movement necessary to account for both chloride and deuterium oxide are being absorbed simultaneously, the 1st and 3rd along their conc. gradients and the 2nd against a gradient, their respective absorption rates indicate that simple diffusion plays a minor role except in the case of deuterium oxide. The known facts of uni-univalent salt impoverishment by the intestine can be accounted for on the basis of the fluid circuit mechanism if corrections for simple diffusion at slow rates of absorption are taken into consideration.—Author (courtesy of Biological Abstracts).

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## Calcium Gluconate Effervescent (FLINT)

FLINT, EATON & COMPANY  
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KARAKI, H.

*Experimentally Induced Proliferation of Bile Ducts in Adult Rabbits. Trans. Soc. Path. Japonicae, 28:275-277, 1938.*

By placing a loose ligature around the liver of adult rabbits the bile ducts become first dilated in the portion proximal to the ligature. A new formation of small bile ducts then occurs, in which young connective tissue (mucous tissue) proliferates. The new formation of bile ducts is most pronounced after 9 to 14 days of ligation, at first as thin elastic fibers, but on the 29th day the connective tissue bundle becomes quite thick.—K. Kato (Courtesy of Biol. Abst.).

KUNERTH, BERNICE L. AND PITTMAN, MARTHA S.

*A Long-time Study of Nitrogen, Calcium and Phosphorus Metabolism on a Low-protein Diet. J. Nutrition, 17(2):161-173, 1939.*

N, Ca and P balance studies of fifteen 3-day periods were made on three normal women subjects of 23 and 24 years on a diet supplying 45 cal. per kgm. and 75% of the protein requirement, 85% of it as beef round. All subjects showed considerable variation in retentions. The average N balances were positive. Levels of 92 and 97% respectively of 0.68 gm. Ca and 1.32 gm. P per 70 kgm. were insufficient to prevent losses. Retentions of both tended to be parallel but P was better used than Ca. No definite cyclic tendency toward retention was evident.—Authors (Courtesy Wistar Bibl. Serv.).

MARTIN, GUSTAV J.

*Studies of Fat-free Diets. J. Nutrition, 17(2):127-141, 1939.*

With a highly purified fat-free diet, scaliness of the hind feet and sub-

Why these specially  
homogenized vegetables\*  
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These experiments were reported in the September issue of *The Journal-Lancet*. For free reprint, write Libby, McNeill and Libby, Research Laboratories, Department AD-10, Chicago.

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digestion*  
**IS RAPID**

In three series of comparative tests, the average time for gastric digestion of specially homogenized vegetables was approximately one-half that necessary for digestion of strained vegetables. (Emptying times of the stomach were recorded using fluoroscopy and roentgenograms.)

*Energy  
expenditure*  
**IS LOW**

Experiments also showed that the digestion of specially homogenized vegetables required an energy expenditure of only 43 per cent of that necessary for digestion of strained vegetables.

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  - Spinach
  - Peas
- 5 Vegetable Combinations
- A Cereal Combination
- 2 Fruit Combinations
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**SPECIALLY HOMOGENIZED VEGETABLES**

normal weights were indications of a fatty acid deficiency, but with great biological variations. Curative and prophylactic supplements of methyl linoleate produced comparable results as regards maximum average weights attained, thus indicating the absence of permanent damage. The minimum level of methyl linoleate for optimal growth effects was tentatively placed at or below 1 drop (30 mgm.) per day per rat. The inability of methyl linoleate to supplement methyl linoleate was proved. Rats fed a highly purified synthetic diet, complete in all known dietary essentials, cease growth at subnormal weights, but showed positive growth response to supplements of brain and liver. — Authors (Courtesy Wistar Bibl. Serv.).

PITTMAN, MARTHA S. AND KUNITZ, BERNICE L.

*A Long-time Study of Nitrogen, Calcium and Phosphorus Metabolism on a Medium-protein Diet. J. Nutrition, 17(2):175-185, 1939.*

Data on four normal young women on a diet supplying 40 to 45 cal. per kgm. and approximately twice their requirement of protein (194%) were contrasted with those of a similar study on a lower level of protein. The apparent coefficient of digestibility of the N increased due to decreased fecal

and increased urinary N. The average N retention for all subjects was high, P intakes were slightly lower than in the low protein study but retentions were better, Ca remaining slightly negative and P becoming positive. The tendency to variation in all retentions was not changed by the increased protein although the utilization was improved and did not decrease in the more mature subject (31 years). With the increased protein the Ca level was inadequate to maintain equilibrium during the 45-day period. — Authors (Courtesy Wistar Bibl. Serv.).

SWAMINATHAM, M.

*The Relative Amounts of the Protein and Non-Protein Nitrogenous Constituents Occurring in Foodstuffs and Their Significance in the Determination of the Digestibility Co-efficient of Proteins. Indian J. Med. Res., 25 (4):847-855.*

By the Stutzer method, the average amounts of non-protein N, expressed as % of total N, found in different foodstuffs were as follows: Cereals 5%; pulses 9%; nuts and oilseeds 5%; condiments 6%; vegetables 14% and milks 9%. The common use of the factor 0.25 is thus not fully justified, and the co-efficient of digesti-

bility of the protein may be underestimated, because of the presence of varying amounts of poorly available non-protein N. — M. Swaminathan (Courtesy of Biol. Abst.).

VIRTUE, ROBERT W. AND DOSTER-VIRTUE, MILDRED E.

*Studies on the Production of Taurocholic Acid in the Dog. III. Cystine Disulfide, Cysteine (2):431-437, 1939.*

Fasting bile fistula dogs were fed 2.8 gm. of cholic acid daily to deplete their livers of taurine. Equivalent amounts of cystine disulfide given orally or parenterally, cysteine sulfonic acid injected subcutaneously, or cystic acid given by mouth with the cholic acid, usually on the 3rd day of the fast, increased the excretion of taurocholic acid. Cystic acid was especially effective. Each of the 3 substances were apparently changed to taurine by the dog. Nearly all of the extra urinary S from the cystine disulfide and the greater part of the extra 3 from the cysteine sulfonic acid were found in the sulfate fraction of the urine. Very little of the S of the cystic acid, however, was oxidized to sulfate. — R. W. Virtue (Courtesy of Biol. Abst.).

UNNA, KLAUS.

*Studies on the Toxicity and Pharmacology of Nicotinic Acid. J. Pharmacol. and Exp. Therap., 65(1):95-103, 1939.*

Nicotinic acid, Na nicotinate and nicotinic amide as investigated in mice, rats, chickens and dogs have very low toxicity, the L.D. 50 in mice after subcut. and oral adm. being 4 g. and 5 g./kg. Daily feeding of dogs with 2 g./kg. of nicotinic acid as Na nicotinate over 35 days failed to produce toxic symptoms; 30% of such a dose was excreted unchanged in the urine after 24 hours. No effect could be shown on metabolism (rats), or on respiration and circulation (rabbits, cats, dogs). — K. Unna (Courtesy of Biol. Abst.).

BARCLAY, A. E.

*The Practical Importance of Mechanics in Digestion. Am. J. Roentgenol. and Radium Therap., 40(3):325-334, 16 figs., 1938.*

By means of a diaphragm, light and mirror system introduced through the nose, records of varying pressure in the mouth and nasopharynx during the act of swallowing were registered. Observations made in this manner were supplemented by X-ray films and (in animals) by roentgen cinematography. For the stomach and intestines, X-ray examination alone was relied upon. The conclusion was reached that peristalsis is only one of the possible mechanisms by which

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To aid normal bowel function, KARAJEL offers the physician a choice of four types of bulk medication:

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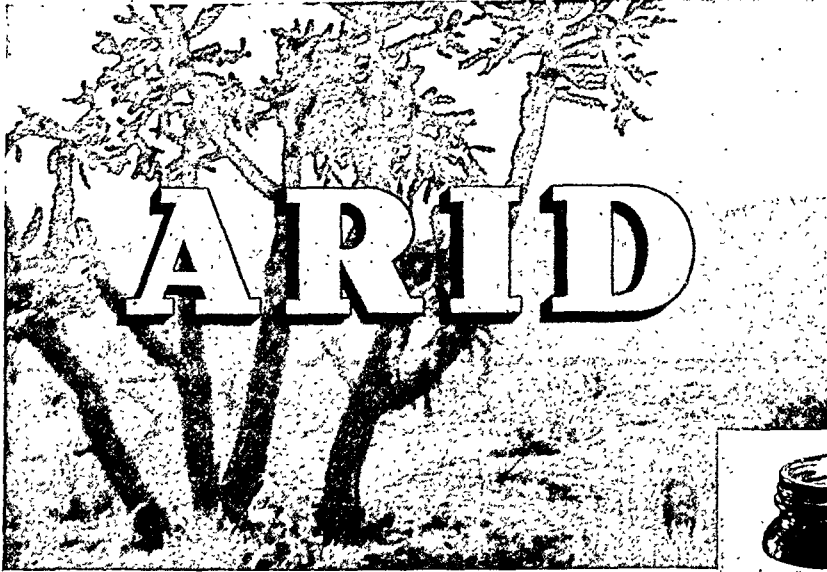
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REPRINTS of the Editorial "Aids to Normal Bowel Function," "Amer. J. Dig. Dis.," March, 1939, J. A. Bergen, M.D., will be supplied on request.

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Dry, dehydrated fecal masses are typical of the resistant cases of constipation. For those cases where the mild stimulation of bulk alone is unavailing—such as are encountered in pregnancy and senility—the Stearns Laboratories present

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The smooth water-controlling bulk of Mucilose allied with a gentle tonic laxative. Mucilose itself is a hemicellulose obtained from the *Plantago loeflingii* with an unusual ability to swell in the presence of liquid and form a mucilaginous mass which eases natural elimination.

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**Dose:** One to two teaspoonfuls, followed by copious water.



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**Requires no cooking.** Pablum can be prepared quickly and conveniently at the office or shop simply by adding milk or cream and salt and sugar to taste. Can also be used in a variety of appetizing dishes to enhance their vitamin and mineral values. Pablum (Mead's Cereal thoroughly cooked) consists of wheatmeal (farina), oatmeal, cornmeal, wheat embryo, alfalfa, yeast, beef bone, sodium chloride and reduced iron.

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Konsyl can be used regularly until natural bowel habit is established, and then used only at times when there is any recurrence of constipation for a short time, when perhaps the patient has been under more stress or strain, for most cases of constipation are spastic or nervous and related to hurry and strain.

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substances are propelled through the digestive tract, and that practically it is often a reserve mechanism, for use after normal ones have failed. Changes in pressure, and active muscular contraction are the usual agents.—E. H. Quimby (Courtesy of Biol. Abst.).

BROWLEY, R. E. AND SEDWICK, H. J.  
*Studies Concerning the Oral Cavity and Saliva. IV. Calcium (1) Calcium Content of Resting and Activated Saliva of Children. J. Dental Res., 17(6):477-492, 1938.*

The Clark-Collip modification of the Kramer-Tisdall method for serum Ca was used in making detn. All samples of saliva were collected in the morning at least 1 hour after breakfast. No significant differences were found between the mean Ca values either in the resting or activated saliva according to sex, nor between the means for the age groups (1-6, 6-10, 10-15, 15-20). There is a difference of 0.66 mg. of Ca per 100 cc. between the means of resting and activated saliva. Taking all factors into consideration it may be assumed that the standard range for salivary Ca for children between 6-18 is: resting saliva, 5.1-8.6 mg. cal. per 100 cc.; activated, 4.5-8.0 mg. An extensive bibliography is included.—D. C. Lyons (Courtesy of Biol. Abst.).

CAMERON, G. R. AND DE SARAN, G. S. W.

*A Method for Permanently Dissociating the Spleen from the Portal Circulation (the "Marsupialised" Spleen) and its Use in the Study of Experimental Liver Cirrhosis. J. Path. and Bact., 48(1):41-47, 2 pl., 1939.*

An extra-abdominal spleen enclosed in a vascularized fibrous pouch between the skin and the ant. abdominal muscle of rats, freed from portal connections, is produced by a 2-stage operation. Pulp hyperplasia occurs in such a "marsupialised" spleen during the course of toxic cirrhosis induced by CCl<sub>4</sub>, and is therefore independent of portal obstruction. Direct support is thus provided for the belief that cirrhosis splenomegaly is the result of (a) pulp hyperplasia, (b) portal obstruction.—Auth. (Courtesy of Biol. Abst.).

In the Western Journal of Surgery, Obstetrics and Gynecology (1939) Miller and Crombie reported a study of twenty-five children who in the years from ten to fourteen had no dental caries. Their impression was that contributing factors were (1) good family history, (2) breast feeding, and (3) the absence of serious illness in childhood. Irregular denti-

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Ralston Wheat Cereal contains no other additional food elements than those found in natural whole wheat

Mother Nature herself enriches Ralston with a bountiful supply of vital food properties which she stores in pure whole wheat. None of these important properties are removed or altered in the milling process except that the coarse outer bran layer is removed. The only enrichment is the addition of wheat germ, a rich natural source of vitamin B<sub>1</sub>. Even the flavor, so universally praised, is Nature's own!

## Valuable natural food properties found in Ralston

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Fat . . . . .	2.0
Carbohydrates . . . . .	72.0
Moisture . . . . .	9.5
<b>MINERALS:</b>	
Iron . . . . .	.004
Phosphorus . . . . .	.4
Calcium . . . . .	.04

An average serving (20 grams) of Ralston contains about 30 International Units of vitamin B<sub>1</sub>. In addition, it is an excellent source of vitamins E and G and supplies natural bulk.



Widely prescribed at the time doctors recommend a change from starting cereals.

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...natural wheat cereal naturally fortified with added wheat germ for extra vitamin B<sub>1</sub>

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tion and poor dental hygiene didn't seem to do any harm to the teeth of these fortunate children.

W. C. Alvarez, Rochester, Minn.

In the Presse Médicale for July 15, 1939, V. Climesco, P. Sarbu and S. Roman state that in the case of a girl of twelve with megacolon, spinal anesthesia gave good bowel movements for two weeks. A second injection relieved the situation for four months.

W. C. Alvarez, Rochester, Minn.

In the British Medical Journal for May 27, 1939, C. H. Osborn suggested that a better relaxation of the abdominal muscles can be secured during physical examination if the patient is put in the usual position with the feet on the table near the buttocks and is then asked to lift his sacrum an inch off the table. It is claimed that in this way a very helpful degree of relaxation can be obtained.

W. C. Alvarez, Rochester, Minn.

RENTZ, ED.

*Unwirksamkeit von Acetylcholin und Histamin auf den Darm vom Darmlumen aus. Arch. Exp. Path. u. Pharmacol., 191(2):183-191, 8 figs., 1938.*

Moderate concns. of acetylcholine in the lumen of the guinea pig intestine in situ (Straub's technique) did not affect the motility. Abnormally high doses (0.1 g. per kilo) caused peristalsis, when the critical conc. reached the neighborhood of the Auerbach plexus. Using the mouse intestine as test object (Kahlson's method) it was seen that the acetylcholine introduced into the guinea pig intestinal lumen disappeared completely in the first half hour. Histamine was not active from the lumen of the intestine. Removed from the intestine and tested on a strip of isolated small intestine (Magnus method) it acted very powerfully at concs. 3000 times weaker than that inactive within the lumen of the intestine. If histamine was injected into a closed loop of intestine, in contrast to acetylcholine, it did not disappear fully from the content of the loop in 2½ hours. In contrast to acetylcholine and histamine, pilocarpine or morphine (both best at 1 mg. per kilo) were found active when introduced into the lumen of the intestine. Injected into the lumen of the colon (according by Straub's method) they were effective in about 2-3 minutes, and also caused changes in the motion of the small intestine after about 10 minutes, though they could only reach this portion of the gut by absorption into the circulation. — (Courtesy of Biol. Abst.).

TO TEMPT THE APPETITE OF . . .

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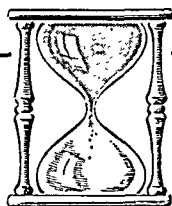
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# Who Dares Predict the Events of 1940?



IN WORLD AFFAIRS, military and political, there is little of which we can be sure. But happily in other fields there are some things of which we can be certain.

Medicine will continue to advance in its march on disease. Nutrition will more clearly light the way to optimal health through food. In the field of food in 1940, Pet Milk will surely play a more important role than ever before.

During the past year physicians prescribed more Pet Milk for the diets of infants and adults than had been prescribed in any previous year of our fifty-five years in business. Indications point to still more extensive use in 1940.

The record of last year is gratifying; the prospects for this year, pleasing—not only because of increased sales, but

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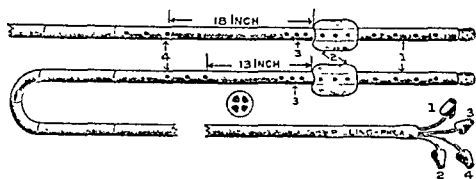
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Through many years of clinical use, Valentine's Meat-Extract has proved to be easily retained, and useful in many cases with impaired digestion or assimilation.

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of Digestive Diseases" October, 1939.

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MAGYAR, IMRE.

*Untersuchungen über die Wirkung von Vitamin B auf  
den Kohlehydratstoffwechsel. Zeitschr. Ges. Exp.  
Med., 104(4):495-503, 1938.*

The blood sugar was studied in non-diabetic and diabetic patients after administration of insulin with and without Vitamin B<sub>1</sub> (beataxin) and in rabbits which had received dextrose, galactose, insulin and Vitamin B<sub>1</sub> in various concs. and combinations, and atropine in order to determine the influence of the vagus nerve. Fasting blood sugar is not influenced by Vitamin B<sub>1</sub>; insulin hypoglycemia is increased in depth and duration by Vitamin B<sub>1</sub>, the hyperglycemia after dextrose and galactose administration is inhibited, its duration reduced.—M. Samter (Courtesy of Biol. Abst.).

ALLEY, ARMINE AND BABKIN, B. P.

*The Effect of Histamine and Pilocarpine on Gastric  
Secretion Inhibited by Fat. Arch. Internat. Phar-  
macodyn. et Thé., 61(1):99-108, 1 fig., 1939.*

Inhibitory effects of fat on gastric secretion are more marked in the Armour pouch than in the Pavlov pouch. Histamine or pilocarpine provokes copious gastric secretion in both preparations after inhibition of fat. Though the volume of secretion elicited by pilocarpine in the fat-inhibited pouch is equal to control pilocarpine secretion, the peptic activity is less.—G. A. E. (Courtesy of Biol. Abst.).

## CONNOTATIONS

H. J. SIMS

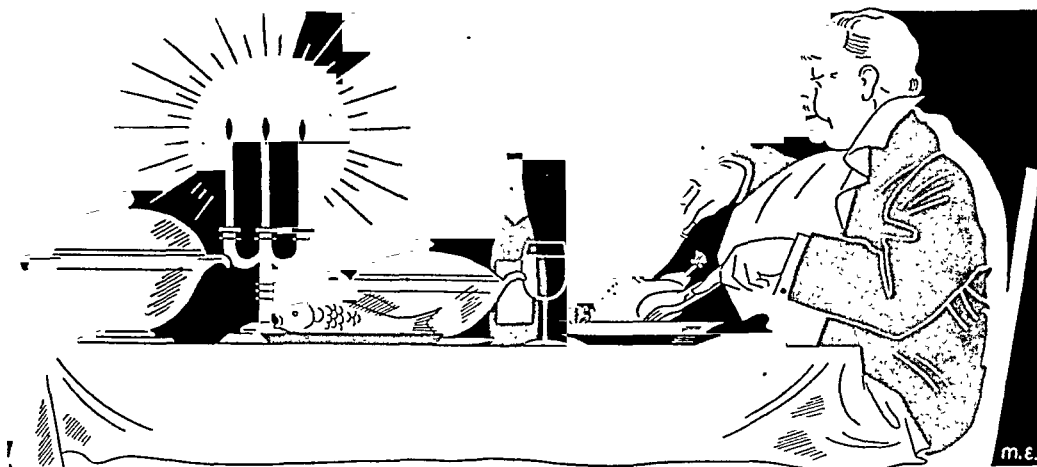
Denver, Colorado

Weir in 1902 anchored the appendix to an incision in the anterior abdominal wall for the purpose of irrigating the cecum and colon.

Haller in 1743 first recognized the existence of the carotid body. He named it "intercarotid ganglion," thus classifying it as a nerve structure. Arnold in 1865 gave it the name of "intercarotid arterial glomeruli" because of its resemblance to glomeruli. Schaper and Stilling in 1892 described it as a blood vessel gland, analogous to the adrenal gland. Marchand published the first case report of a tumor involving this structure. Paltauf in 1892 reported 4 cases. Balfour and Wildner in 1914 reported an instance and stated that 35 cases had appeared in the literature since the publication of Paltauf's article. These investigators appended 53 references. Meuron in 1886 and Robl in 1889 shared in their views that the carotid body was derived from the third or fourth branchial sympathochromaffin system anlage which passes from the upper sympathetic ganglion.

The earliest writing of the appendix is that by Morgagni in 1719. He stated that the vermiform appendix was not only absent in many animals but had been found deficient in man. Massa and Hunter reported similar anomalies. The first authentic report of congenital absence of the appendix was made by Meckel in 1812. His observation was made on a cadaver in which the cecum and the surrounding tissues were normal. Puchelet in 1832 described a case, under the title of perityphilitis, which was probably a result of appendicitis. The case reports of Tarenetsky and Lafforgue are problematical.

Melier in 1827 reported 8 cases of peritonitis, 3 of which he described as representing perforation of the appendix. Melier considered the cause, character, and consequences, for he stated "if it were possible to establish with certainty the diagnosis of this affection we could see the possibility of curing the patient by operation." Hancock in 1848 operated on a case of appendicitis and advocated early operative interference. Lewis in 1856, Bamberger in 1858, and Leudet in 1859 insisted on early surgical intervention. Noyes writing in 1882 reported the first successful appendectomy during an acute attack of appendicitis.



## THE DIARY OF DR. PEPYS

*Up betimes and to the office, there to find before me the Banker Castlemaine who, at the instant of my entrance, declareth himself distressed.*

*A pompous gentleman, much given to publick dining. He hath for three nights sat late at banqueting, which he will never forego.*

*I did prescribe Cal-Bis-Ma for him for the quick relief he finds in this fine powder.*

... Dr. Pepys is right. When hyperacidity gives rise to gastric distress, Cal-Bis-Ma will give prompt and prolonged relief. Sodium bicarbonate and magnesium carbonate for quick action; calcium carbonate and bismuth for prolonged effect, and colloidal kaolin to adsorb the gas formed in the neutralization process. These ingredients, carefully matched for density, are held together in a colloid base that assures uniform distribution and dosage. Trial supply gladly sent to physicians.

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Powder in tins of 1¼, 4 and 16 ounces; tablets in boxes of 30, bottles of 110

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The Acid-Aqueous-Glycerin Extract of  
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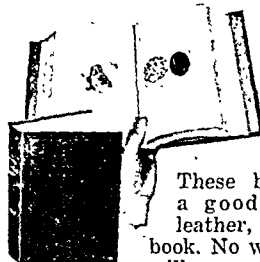
GASTRON, by itself or in combination, is indicated in hypoacidity, anorexia, the debilitated digestion of convalescence and old age, as accessory in the treatment of anemias, and in nausea, particularly of pregnancy.

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# The Gastro-Ileac Reflex: Further Experimental Observations

By

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and

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ROCHESTER, MINNESOTA

THE occurrence of a motor response in the lower part of the ileum following the ingestion of food is well established both in clinical and in experimental fields.

Evidence was presented in a previous study (3), which seemed to indicate that the response in the ileum depends for its mediation on the continuity of the intestine and not on the extrinsic motor nerves. A logical corollary of this conclusion appeared to be the investigation of possible motor responses at higher levels in the small intestine and the correlation of their time relationships with those already noted for the lower part of the ileum.

We were further interested to find out whether receptors other than those in the stomach were capable of initiating the response, and whether feeding by a duodenal fistula would be followed by a motor response lower down in the small intestine, a suggestion made by Hinrichsen and Ivy (1931).

## METHODS

Exteriorized loops of small intestine in continuity enclosed in bipedicle tubes of skin were prepared at various levels of the small intestine and colon in trained dogs. In one animal a fistula of the duodenum was prepared after the technic of Mann and Bollman.

The experimental procedure was the same as that described in the previous study (3) and incorporated the graphic recording of the activity of the exteriorized loops before, during and after the ingestion of a standard meal. The time from the beginning of the meal to the occurrence of the motor response in the loop was taken as the time relationship of the response. As noted in the previous paper, to permit of constant results, the animals must be fasted for forty-eight hours before the experiment is performed.

## RESULTS

Twenty-five experiments were carried out in animals with exteriorized loops of small intestine at various levels. In dog 1 the loop was prepared in the jejunum immediately below the ligament of Treitz and in dog 3, as a control, a loop of ileum was prepared just above the ileocecal junction.

In the animals with the jejunal loops as in the animal with the ileac loop a well-marked motor response following feeding was noted in all of the experiments (Table I and Fig. 1). The response in the jejunal loops was similar to that in the ileac loops except that it occurred more rapidly as a rule in the former than in the latter. The average time of the response in the highest jejunal loop was 1.2 minutes after the ingestion of the meal, in the other jejunal

loop 1.4 minutes and in the low ileac loop five minutes. The figure noted for the ileac loop is similar to that observed by Hinrichsen and Ivy and by us in the previous study (3). It was noticeable that there were greater variations in the time relationships of the response in the ileac loop than in the jejunal loops. Thus, while in the highest jejunal loop the time of occurrence of the motor response after the meal did not vary from day to day more than from one to 1.5 minutes, that in the low ileac loop showed variations from 2.5 to eight minutes.

In searching for an explanation for this comparatively wide variation, a number of observations seemed to indicate that the answer lay in the distance of the ileac loop from the pylorus. In the first place since the response appears to depend for its mediation on

TABLE I

*Time from feeding to motor response in various levels of the small intestine*

Dog	Level of Exteriorized Loop of Intestine	Average Time, Minutes	Variation, Minutes	Number of Experiments
1	Jejunum, immediately below ligament of Treitz	1.2	1-1.5	9
2	Jejunum, 60 cm. below ligament of Treitz	1.4	1-2.5	10
3	Ileum, immediately above ileocecal junction	5	2.5-8	6
Total number of experiments		25		
Observation period		...	6 months	

the continuity of the intestine, it is reasonable to suppose that the response is propagated down the intestine. In the second place, since the response occurs more rapidly in the jejunum than in the ileum, one would naturally suspect that it had reached the jejunum before passing down to the ileum. Finally, the more constant time relationships of the jejunal responses as compared with these noted in this and the previous study in the ileum, can be reasonably explained on the basis of the greater distance of the ileac loops from the pylorus and the varying rates at which propagation of the response takes place.

Whether this explanation is the correct one or not, it led us to observe the motor response in an animal in which two exteriorized loops had been prepared at different levels in the small intestine. If the motor response is conducted down the length of the small intestine, one would expect that it would make its appearance in the higher loop before appearing in the lower loop. The results in this preparation showed

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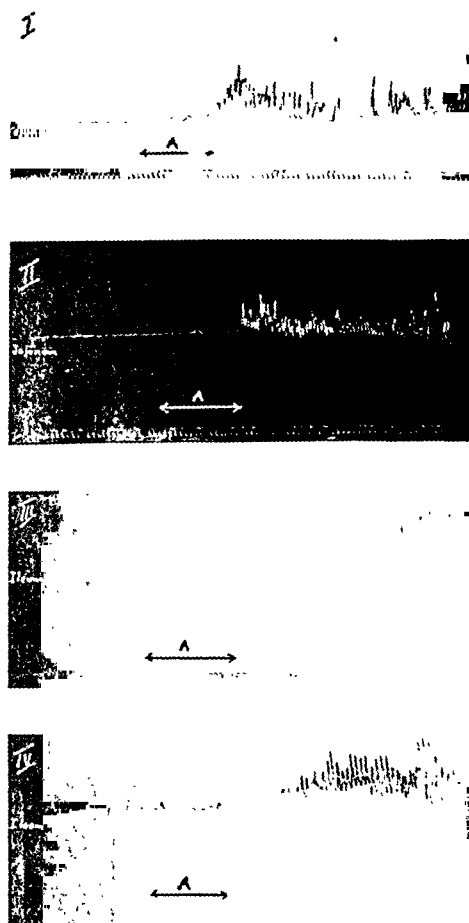


Fig. 1. Motor response to feeding in exteriorized loops of jejunum and ileum. Animal fed at A. Time in five second intervals. It will be noted that the response occurs more rapidly in the jejunal than in the ileal loops.

this actually to be the case (Fig. 2). The average time of the response in the higher loop was 7.5 minutes while that in the lower loop was 9.2 minutes (Table II). Both these figures represent a considerably longer latent period than was observed as a rule in analogous loops in other animals. No explanation other than biologic variation is offered for this finding.

A consideration of the time interval between the appearance of the response in the upper loop and its appearance in the lower loop is of interest. Since the distance between the two loops was known to be 50 cm., some idea of the rate of propagation of the response in the ileum can be obtained. The time intervals noted were from 0.5 minute to two minutes which would give a calculated rate of progress of from 1.7 to 0.4 cm. per second, figures which are approximately comparable to those arrived at by calculation on the basis of the distance of a single loop from the pylorus.

**Feeding by duodenal fistula.** A control series of experiments was carried out in an animal with an exteriorized loop 25 cm. above the ileocecal junction. The average time of the motor response after normal feeding was 4.6 minutes. A duodenal fistula was then es-

tablished and the experiments were repeated. One hundred cubic centimeters of a milk and syrup mixture was run into the duodenum by gravity. A motor response following duodenal feeding of this character was noted constantly in the lower ileum, the average time of the response being 2.8 minutes after the instillation of the mixture (Table III).

It is perhaps worth mentioning that in this preparation it is necessary to be certain that the catheter used for the introduction of the mixture has actually

TABLE II

*Time from feeding to motor response in two exteriorized loops of intestine in the same animal*

Dog	Level of Exteriorized Loop of Intestine	Average Time, Minutes	Variation, Minutes	Number of Experiments
4	Ileum 75 cm. from ileocecal junction	7.5	2.5-11	6
	Ileum 25 cm. from ileocecal junction	9.2	3-13	

Maximum interval between responses... 2 minutes

Minimum interval between responses... 0.5 minute

passed into the duodenum. At the outset of experiments, difficulty was experienced in this regard. If the tip of the catheter merely lies in the afferent limb of the fistula, the latter becomes filled with the mixture, the mixture runs in slowly, reflux occurs at the stoma and negative results as to the motor response in the ileum occur. If the tip of the catheter actually lies in the duodenum the mixture runs in easily, no reflux occurs and a positive motor response occurs in the ileum.

TABLE III

*Time from feeding to motor response in exteriorized loop of ileum by normal and duodenal fistula feeding*

Dog	Method of Feeding	Level of Exteriorized Loop of Intestine	Average Time, Minutes	Variation, Minutes	Number of Experiments
5	Normal	Ileum 25 cm. above ileocecal junction	4.6	3-9.5	6
	By duodenal fistula		2.8	2.5-4	8

Total number of experiments... 14

It is noteworthy that the motor response occurs on the whole more rapidly after feeding by the duodenal fistula than by the mouth.

**Effect of section of the intestine.** The observations in the preparations described appeared to indicate that after the ingestion of food a wave of activity passes down the length of the small intestine. We therefore thought it of interest to investigate the effect of section of the intestine orad to the loop and resuture in such a way as to prevent at least im-

mediate union of the muscular coats and the intrinsic enteric plexuses.

This was accomplished by sectioning the intestine and invaginating the upper end into the lower end for a distance of about 1 cm. (Fig. 3). At the point of entry of the upper into the lower end a layer of silk seromuscular sutures was inserted, using three stay sutures as employed in end-to-end anastomosis of blood vessels. Since the upper end projected into the lumen of the lower end for a distance of about 1 cm. and since for this distance mucosa was apposed to serosa, it was felt that functional union would be delayed for a considerable period.

The first experiment was carried out five days after the operation. The result was a well-marked motor

that seen in the small intestine, particularly with regard to time relationships, two animals were prepared with exteriorized colonic loops enclosed in skin tubes. In one the loop was prepared in the proximal part of the colon 10 cm. from the ileocecal junction, in the other in the distal part of the colon 35 cm. from the ileocecal junction. It is perhaps worth noting that the preparation of exteriorized colonic loops enclosed in skin tubes is much less easy than the preparation of similar loops in the small intestine. The colic vessels with the mesocolon are so short that it is difficult to mobilize the colon sufficiently without disturbing its nerve and blood supply. For this reason it is not possible to obtain nearly as long loops in the colon as

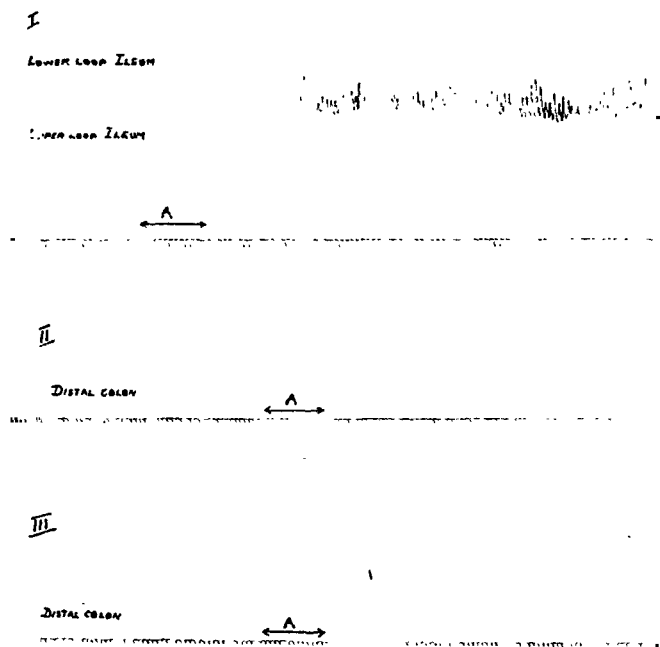


Fig. 2. I. Motor response to feeding in two loops of ileum at different levels in the same animal. It will be seen that the response occurred in the upper loop two minutes before appearing in the lower loop. Time in five second intervals. II and III. Motor response to feeding in the distal part of the colon. Animal fed at A.

response in 4.5 minutes. Eight experiments were carried out in this preparation with similar results (Table IV). The average time of the response before section of the intestine was five minutes after the meal while after section of the intestine and reanastomosis it was 5.5 minutes.

Since the exteriorized loop in this preparation, though mechanically in continuity, was in all likelihood cut off from impulses conducted down the intestine in the myenteric plexus and since in the previous study motor responses did not occur in loops isolated from the rest of the intestine, we were compelled to conclude that mechanical continuity of the intestine is the main factor concerned in the mediation of the motor response.

*Motor responses in the colon.* In order to correlate the well-established motor response in the colon to

were used in the small intestine and visual analysis of activity is difficult.

Both the proximal and distal colonic loops showed a similar type of tracing, namely slow contractions at the rate of about one to two per minute and in both loops the activity was periodic. The difference between the two loops in respect to activity was in the periods of quiescence which intervened between the periods of activity. In the proximal part of the colon the periods of quiescence were relatively brief, from five to fifteen minutes, whereas in the distal part of the colon these quiescent periods were much more prolonged, of the order of thirty minutes to two hours. This observation, that the proximal part of the colon exhibits greater activity than the distal part, has been made by other observers (2).



After feeding, the distal colonic loop showed a constant motor response, often accompanied by the passage of flatus, from two to seven minutes after the meal (Fig. 2, Table V). These figures are comparable to those noted for the ileum. The proximal colonic loop on the other hand did not show such constant results. In only one of the ten experiments performed in this preparation was a definite motor response observed. The commonest result noted was that the activity was unaffected by feeding (six experiments). On three occasions the activity appeared to be diminished temporarily after feeding. Why the proximal part of the colon should behave differently from the distal part, it is difficult to say. The different embryologic development, function and nerve supply have been cited by other investigators who have made similar observations (2, 6).

### COMMENT

The constancy of the results in the animals with exteriorized jejunal loops indicates that the motor response to feeding previously described for the ileum of man by Hertz and for the ileum of the dog by several observers (1, 2, 5), which has been termed the gastro-ileac reflex, also occurs at higher levels in the small intestine.

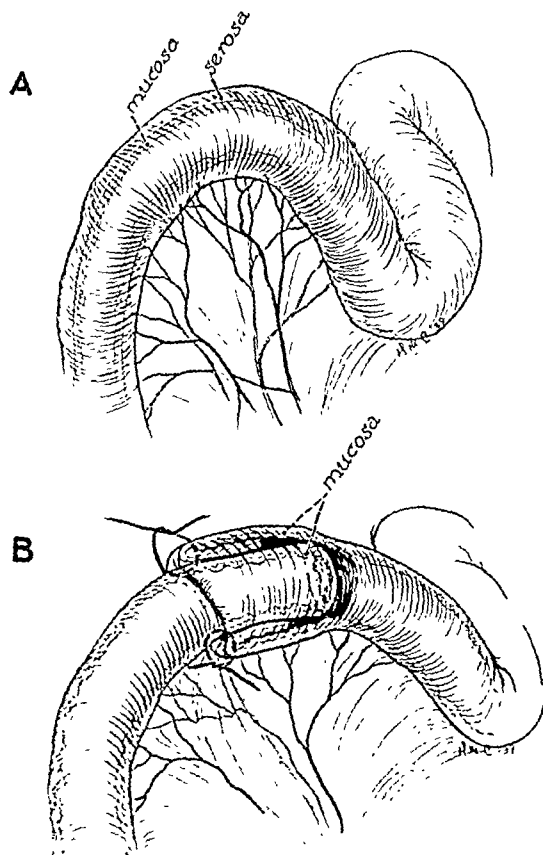


Fig. 3. Technic of section of the intestine and reanastomosis in such a way as to prevent at least immediate union of the intrinsic enteric plexus and muscular coats. It will be observed that serosa is opposed to serosa at the line of suture.

The fact that the jejunal response occurs more rapidly than the ileac response together with the fact that isolation of the loop abolishes the response seemed to suggest that some form of motor activity passes down the length of the small intestine after feeding. Additional evidence for this concept was obtained in the animal with two exteriorized loops, the response appearing in the upper loop before passing on to the lower.

It must be emphasized that the evidence for the existence of a wave of activity of this character is purely

TABLE IV

*Time from feeding to motor response in ileum before and after section and reanastomosis of intestine orad to the exteriorized loop*

Level of Loop	Period of Observation	Average Time, Minutes	Variation, Minutes	Number of Experiments
Immediately above ileocecal junction	Before operation	5	2.5-8	6
	After operation	5.5	3-8.5	8

Total number of experiments .. 14

circumstantial and the apparent differences in the rate of propagation may depend on variations in the time of initiation of the activity after ingestion of food. Direct evidence must await the elaboration of a technic whereby the whole length of the small intestine in the fasting conscious animal and its response to feeding can be visualized. The results noted after section and reanastomosis of the intestine indicate that a breach in the myenteric plexus orad to the loop does not prevent the propagation of the response. This is of interest in view of the fact that Alvarez has

TABLE V

*Time from feeding to motor response in proximal and distal parts of the colon*

Dog	Level of Exteriorized Loop of Colon	Average Time, Minutes	Variation, Minutes	Number of Experiments
7	35 cm. from ileocecal junction	3.8	2-7	8
6	10 cm. from ileocecal junction	no response 3	..	9 1

Total number of experiments....18

noted that a peristaltic rush in the rabbit is capable of passing an interposed glass tube by virtue of the displacement of contents and distention which precedes the rush.

Little comment is required on the results noted after feeding through a duodenal fistula. They indicate that the presence of food in the duodenum is capable of exciting the response.

The experiments performed in the animals with colonic loops are on the whole in agreement with the observations of others who used different technics.

The evidence for the existence of a wave of activity passing down the small intestine is so strong that we were tempted to suspect that the gastro-colic reflex was simply a continuation of this wave along the colon. Such, however, does not appear to be the case. The evidence indicates that the proximal part of the colon does not share in the motor response, at least not to the degree that the small intestine and the distal part of the colon do. The time relationships of the response in the distal part of the colon are similar to those noted in the ileum, a point which would render unlikely the possibility of propagation of the response from the ileum along the colon.

It appears likely therefore that the response of the small intestine and the response of the colon are not part of the same excitatory process transmitted along the intestine.

In view of these findings, the question arises as to whether the term gastro-ileac reflex is an accurate one. The term connotes a reaction which is confined to the ileum, whereas in fact the jejunum shares in the reaction as well. Furthermore, the introduction of food into the duodenum is capable of exciting a response indistinguishable from that seen after normal feeding. Finally, it is open to doubt whether the reaction is reflex in nature, at least in the ordinarily accepted meaning of the term. It does not depend on the integrity of the extrinsic motor nerves and the evidence indicates that it is propagated down the length of the small intestine.

### SUMMARY

The activity of exteriorized loops of jejunum, ileum and colon in continuity in trained dogs was studied in relation to feeding.

A prompt motor response following feeding was noted in both the jejunal and the ileac loops. The response occurred more rapidly in jejunal than in the ileac loops. Moreover, in an animal in which two exteriorized loops of small intestine at different levels were prepared, the motor response constantly appeared in the loop at the higher level before appearing in the lower loop.

Feeding by a duodenal fistula gave as constant results as feeding by the mouth. Section of the intestine orad to the loop and reanastomosis in such a way as to prevent at least immediate union of the muscular coats and the intrinsic enteric plexuses, did not prevent the occurrence of the motor response. A constant motor response was noted, after feeding, in the distal part of the colon but not in its proximal part.

The findings are taken to suggest that following the ingestion of food, a wave of activity traveling at the rate of about 1 cm. per second passes down the length of the small intestine. The gastro-colic reflex does not appear to be a part of this excitatory process.

It is suggested that the term gastro-ileac reflex is not sufficiently inclusive.

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## The Use of Hydrated Trisilicate of Magnesium for Peptic Ulcer\*†

By

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with the technical assistance of

BERNARD AARON, Ph.B., B.S.§

THE medical profession was introduced to Hydrated Trisilicate of Magnesium in 1936 by N. Mutch (1, 2, 3) of England. This substance had been known to chemists as one of a number of magnesium silicates which exist in natural states as Fosterite, Serpentine, Talc and Meerschaum. The term Meerschaum (sea foam), indicative of its color and porosity, was applied in 1788 to the naturally occurring trisilicate of Magnesium. In addition to the natural forms of magnesium silicates there are numerous synthetic forms. Mutch studied the antacid properties of the known magnesium silicates and found that synthetic magnesium trisilicate, identical with Meerschaum, had the greatest neutralizing power for mineral acids and in ad-

dition had marked adsorbent qualities. This mineral, previously known as an excellent material for making pipe bowls and cigar holders and used as building stone in Spain and soap in Morocco, was now presented as an antacid for treating peptic ulcer.

After Mutch's report on the powder's clinical efficacy in peptic ulceration, writings by Mann (4), Kraemer (5) and Tidmarsh and Baxter (6) appeared to corroborate his testimony. Eusterman (7), Hunt (8), Hurst (9) and Hardy (10) also commented favorably on the use of magnesium trisilicate for peptic ulcer. Levin (11) and Goldstein (12), on theoretical grounds, tried trisilicate of magnesium in a mixture with other alkalis though I do not believe their clinical results were better than if the powder were used alone.

Mutch had good reasons for adding another antacid to the list already in use for treating peptic ulcer. It causes no toxic effects and does not affect colonic motility. Neutralization of acid proceeds gradually. This

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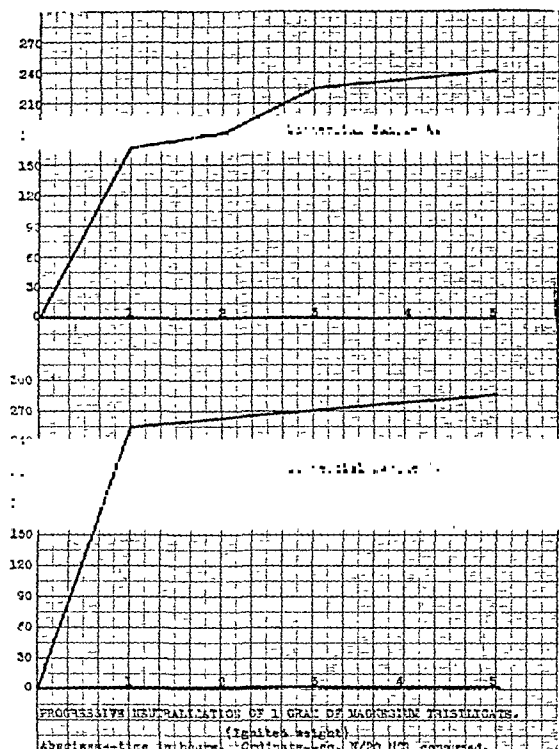


Fig. 1

neutralization lag has distinct value when the powder is used for treating peptic ulcer where acid is being secreted over a period of hours. Neither magnesium trisilicate, nor the hydrated silica ( $\text{SiO}_2$ ), formed by its interaction with HCl, are soluble. Therefore neither the original compound nor this end product can be absorbed from the digestive tract to produce alkalosis. In addition to the neutralization a definite adsorption of acid takes place.

Neutralization, according to Mutch, proceeds as follows:  $\text{Mg}_2\text{Si}_2\text{O}_5\cdot n\text{H}_2\text{O} + 4\text{HCl} \rightarrow 2\text{MgCl}_2 + 3\text{SiO}_2 + (n + 2)\text{H}_2\text{O}$ .

#### EXPERIMENTAL OBSERVATIONS

We verified the neutralization experiments of Mutch. To a series of one gram samples of magnesium trisilicate an excess of N/10 HCl was added, equivalent to approximately 400 cc. of gastric juice (N/20). The mixtures were shaken and at hourly intervals were filtered by vacuum. An aliquot of the acid filtrate was back titrated with NaOH using brom-thymol-blue indicator. The results for neutralization of two commercial samples (A and B)\* are shown in Fig. 1. Note the difference in neutralizing ability between commercial preparations of the powder. Curve B corresponds to the curve obtained by Mutch. While there is a rapid neutralization during the first hour, sufficient magnesium remains unneutralized to continue combining with acid over several hours.

Corresponding to the curves, Table I shows the total volume of N/20 HCl removed (by adsorption and neutralization) from an excess of the acid by one

gram of magnesium trisilicate (on an ignited weight basis) at one and three hour intervals. In addition to the neutralization of acid there is an adsorption of hydrogen ion taking place. This adsorption probably is accomplished by the unreacted magnesium trisilicate and also by the silica ( $\text{SiO}_2$ ) formed after reaction with HCl. On the basis of the equation of Mutch the per cent of acid removed by sample B in one hour is 85% and in three hours 91% and for sample A, 54% in one hour and 75% in three hours. Experiments carried out using stronger concentrations of HCl gave higher results, as stronger acids force neutralization and adsorption.

To determine the acid removed at intervals during the first hour of contact, a series of twelve, one gram samples were treated with an excess of N/10 HCl; at intervals of five minutes. The residual acid was titrated in the presence of the unreacted magnesium trisilicate. This method gives a lower figure at one hour than in the first experiment where the titrations were performed on the filtrate. The first transient blue color appearing throughout the solution was taken as the end point. The reason for a fading end point (according to Mann) is the constant release of adsorbed hydrogen ion. (Adsorbed base is not taken into account). The reacted acid represents both the adsorbed and neutralized acid. The result of these experiments is plotted on Fig. 2. Sample A reacts slower and to a lesser extent than Sample B. This may be due to Sample A being more difficult to wet and penetrate.

To determine the approximate number of cubic centimeters of acid adsorbed the following experiment was performed: At the end of 20 minutes a sample in the presence of excess HCl was titrated with NaOH in the presence of unreacted silicate until a fairly permanent end point was reached. At the end of the same period of time a sample under like conditions was filtered and titrated with NaOH. The unfiltered solution thus contained the acid unneutralized plus the acid adsorbed while the filtered solution contained only the acid unneutralized. The difference in acidity between the two gives the figure for acid adsorbed in 20 minutes. It was found that sample B adsorbed 43 cc. of N/20 HCl and sample A, 40 cc. of N/20 HCl. The acid adsorbed was approximately 10% of the total acid present. The acid neutralized by sample B was 45% of the acid present and by sample A 16% of the acid present.

Mann suggested determining the neutralized acid from the magnesium content of the filtrate at the end of 20 minutes of contact between the trisilicate and the excess HCl. This method would involve an error due to magnesium ion adsorbed and remaining on the filter paper. Mann used normal HCl which resulted in a higher figure. Both neutralization and adsorption are forced by higher acid concentrations. The dilute acid more nearly approaches the physiological. A source for small error in our method occurs from attempting to determine the total acid neutralized in the presence of magnesium trisilicate, because an unmeasurable amount of acid remains adsorbed even after a fairly permanent end point has been reached.

When magnesium oxide or carbonate are used clinically in large doses diarrhea often results. Diarrhea depends on the presence of free magnesium ions in the intestine. Adsorbed HCl will not release mag-

\*Sample A contained approximately 20% water of crystallization and sample B 25%.

nesium ions. Some of the magnesium chloride formed in the stomach by neutralization of trisilicate will be adsorbed in the bowel by either the silica also formed or by unreacted magnesium trisilicate. This factor of adsorption may account for the absence of diarrhea when magnesium trisilicate is employed.

### CLINICAL STUDIES

Trisilicate of Magnesium was prescribed for 135 private and 15 clinic cases of peptic ulcer. Of these I present 90 cases on whom accurate diagnostic and follow-up data are available. There were 5 cases of gastric, 1 marginal and 84 duodenal ulcers. There were 13 female and 77 male patients. The duration of ulcer symptoms for the group varied from 1 month to 30 years with an average ulcer history of 9½ years. The ages for the group varied from 17 to 77 years. These 90 cases have been followed up from 3 to 20 months. 48 cases were followed for more than a year and 70 cases for more than 6 months.

As a whole the group represents long standing, recurrent, severe ulcers. Two patients had had previous acute perforations. In addition to eight of the patients first treated by me for acute hemorrhage, four had had previous severe hemorrhages treated elsewhere. One case had an acute hemorrhage from his ulcer a year after a gastro-enterostomy had been performed. Another patient had had a gastro-enterostomy performed with subsequent gastritis. The gastro-enterostomy was unhitched and shortly afterward the ulcer symptoms returned.

In the majority treatment was carried out according to ambulant routine. The gastric ulcers and

TABLE I

Sample	cc. N/20 HCl Removed	
	One Hour	Three Hours
B	252	262
A	160	222

the marginal ulcer were hospitalized or put to bed at home. The powder was given in gram doses of six times daily. A liquid medication containing Bromide and Tincture of Belladonna was given before the three main meals. Those patients having night pain were instructed to set an alarm at intervals, and, on awakening, to take a glass of milk and a gram of powder. The 8 cases treated for acute hemorrhages were kept in bed and transfused when necessary. Feedings for them were started as soon as active bleeding ceased and Magnesium trisilicate was given in ½ to 1 gram doses every other hour alternating with feedings. All patients were gradually placed on three meals per day with occasional milk feedings at 4 p. m. and at bedtime and the number of powders taken per day was progressively reduced, so that within three to six months many of the patients had eliminated taking of the powder.

All patients were advised to refrain permanently from tobacco, condiments, excess roughage and alcohol. Vacations were advised twice a year and avoidance of fatigue was stressed. An attempt was made

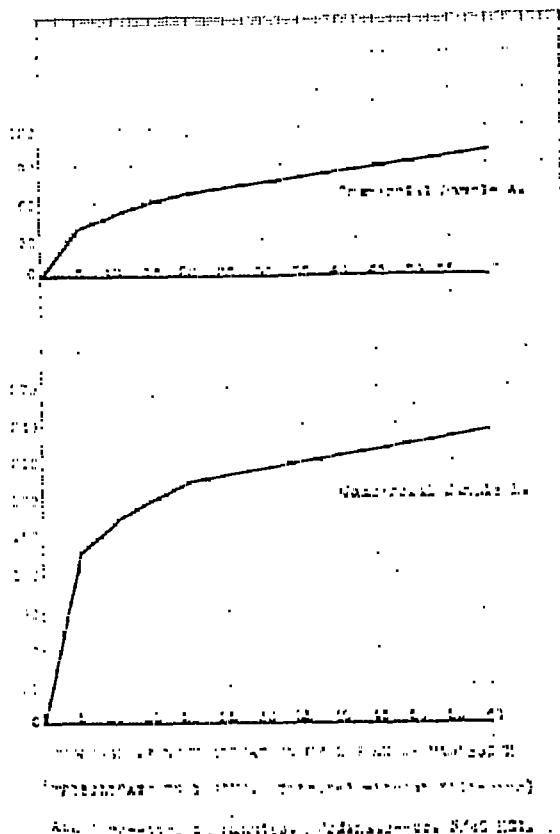


Fig. 2

to help those patients with marital, social, or business problems, to philosophize on their difficulties.

### OBSERVATIONS

In 17 of the 90 patients the use of the antacid did not prove entirely satisfactory. Of these 17, 5 had recurrence of symptoms after disobeying instructions regarding diet and 1 had a recurrence of symptoms for no apparent reason. All six improved promptly on return to a rigid ulcer regimen and 15 grains of the powder six times daily.

This leaves 11 patients out of 90 who were not benefited by the powder. Of these 11, 3 had pyloric obstruction and were cured by gastro-enterostomy and one demanded gastro-enterostomy because he was unwilling to consider staying on a diet for any length of time. One patient, highly neurotic, was not benefited by any antacid medication. On him a subtotal gastric resection was performed with questionable results. One patient with pyloric obstruction has refused surgical intervention and is continuing the use of diet and powder without improvement.

Of the remaining 5 patients, 2 claimed they were relieved more completely by mixtures of other alkalis and one patient claimed he had been feeling better on colloidal aluminum hydroxide.

Of 86 patients in whom successful medical management could have been anticipated this powder used exclusively was efficacious in 79 or 92%. 73 patients (84%) have been entirely free from symptoms and

have had no untoward effects of any kind for from 3 months to over 1½ years.

25 patients who were previously symptom free on colloidal aluminum hydroxide or mixtures of other alkalis, experienced no recurrence nor increase in distress from the change to Magnesium trisilicate. Three patients had marked constipation from aluminum hydroxide which ceased on change to Magnesium trisilicate. Remarkable improvement in the appearance of lesser curvature niches occurred after 4 weeks of modified Sippy treatment using Magnesium trisilicate as the only antacid.

Occasionally a patient complained of loose stools. By slightly reducing the dose this complaint was eliminated in all but 2 cases. Loose bowel movements were not produced by as much as 12 grams per day.

Dosage as large as 12 grams per day produced no change from normal, in the CO<sub>2</sub> combining power of the blood.

### CONCLUSIONS

1. Two commercial samples of trisilicate of Magnesium were analyzed for antacid action. They varied greatly in acid neutralizing ability. The findings in sample B verified the experiments of Mutch.

2. It was found for sample B that, after 20 minutes, 10% of acid present was adsorbed and 45% was neutralized. If percentage was figured from equivalent acid (Mann), the figure for acid adsorbed would be 17.5% and for acid neutralized 61%.

3. Trisilicate of Magnesium was used for 150 patients with peptic ulcer. In a series of 90 cases studied carefully 86 cases could anticipate benefit from medical management. Of these 92% were markedly benefited and 84% kept symptom free for the duration of the study.

4. Trisilicate of Magnesium has no effect on colonic motility in most cases. It produced no discernible toxic effects. It does not affect the acid-base balance of the blood serum.

5. Trisilicate of Magnesium has a use in the treatment of peptic ulcer and will probably replace many antacids now employed.

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## Does Bran Produce Intestinal Obstruction?\*

By

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IN view of the extensive use of bran and its progressive increase, the actual danger of intestinal obstruction from the consumption of bran becomes a question of interest to public health. Hence we have undertaken a search of the world's medical literature on the subject and herewith report the results.

Instances of acute intestinal obstruction are, of course, commonly found in medical literature. Thus Vidgoff (1) reports a series of 266 cases of acute intestinal obstruction and Cornell (2) has collected 235 cases of this kind. In neither of these series is there any reference to a case of food-produced intestinal obstruction nor is there any mention of any case of bran-caused occlusion. This may serve to show that intestinal obstruction due to foods is rare.

Perhaps the most extensive collections of cases of food-produced intestinal obstruction have been published by A. H. Elliott (3) and by F. Leisinger (4), the causes of which we have arranged with the other cases found in world literature in the composite Table I which shows what foods have been found to cause intestinal obstruction. In this table the bran

cases or those allegedly due to bran are italicized. Both Leisinger (who reports 66 total cases) and Elliott (who lists 39 total cases) have each one bran case, and in both reports it is the same case (Fink's); and, as will be seen, this case is not one of bran obstruction.

*Fink's case* (5) (*paralytic ileus without obstruction*). Curiously enough, this one case—that of Fink—listed by both of the above mentioned authors and mentioned over and over again in most of the other articles dealing with the relation of bran to intestinal obstructions, is one of four cases of paralytic ileus reported in 1909 by F. Fink. The following is the literal translation of Fink's report of the case:

"In the fourth the operation revealed a similar condition to that of case 1: namely, great distention of the bowel extending from the stomach down to the colon, injection of the serosa of the bowel and great tension and great swelling and a soggy condition of the wall of the bowel. Having determined that it was *not mechanical obstruction*, the intestine was replaced and the abdomen closed without aid. Without washing of the stomach or the use of enemas the patient recovered. This patient stated that he ate bran in con-

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siderable quantity." Fink also reports three other cases of paralytic ileus, all of whom died; in the bowel of the patient with the worst condition, large quantity of 'unhusked oats was found, while in the other two cases husked oats were considered the cause of the paralytic ileus. In all of these cases the author ascribes the clinical picture to "catarrh produced by excessive fermentation which caused distension of the bowel to such a degree as to produce paralysis of the intestinal innervation and consequent ileus."

These cases certainly can have nothing to do with the way in which bran is employed ordinarily in diet. The allegation that bran had caused the paralytic ileus rests merely upon the statement that the patient "ate bran in considerable quantity!" There was no obstructing mass.

*Case of E. J. Butzke, H. O. Barker, J. R. Boswell and T. E. Drewett (6). (Ulcer-caused impaction).* The authors state that, after reviewing the literature in roentgenology, they "failed to find any reports in regard to the impaction of bran in the gastro-intestinal canal producing shadows on X-ray films." They believe that bran-containing stool impaction produces characteristic shadows that may easily be interpreted as such; but other roentgenologists have since then (1928) not confirmed their observation.

They present a history with photographs taken from X-ray films of two cases recently observed by them. The obvious facts of the history of patient 1 are as follows: That the perforating amebic ulcer was a primary cause of the patient's sickness and that the alleged bran impaction, if there was such a one, was secondary, might teach that, when there is ulceration of the bowel, the use of bran is contraindicated. While this case must be accepted as possibly one of bran-caused obstruction, it should be pointed out that in the condition of the patient's bowel, almost any other food may be retained in such pathologic portion of the intestine.

Unfortunately for the authors' expertness in roentgen diagnosis, it is obvious to an experienced roentgenologist from the published photographs that the mass they mistook as "characteristic for bran impaction" is merely a typical picture of a stool mass in the pelvic colon. Since bran itself is certainly not opaque to the roentgen rays and gives no characteristic shadow, an attempt to diagnose bran impaction by a shadow on the roentgenogram is entirely erroneous.

Nevertheless the authors go so far as to publish pictures of a second case in which there were no symptoms of intestinal obstruction and in which they base their diagnosis entirely on a shadow in the lower pelvis that seemed similar to them to the first case cited. On questioning it was found that the patient had been eating bran for constipation, that he had two good bowel movements that morning and that two enemas removed the "alleged impaction" as was shown by the second roentgenogram. The mass probably would have passed later without any interference whatsoever.

This case cannot be accepted as one of bran obstruction.

*C. B. Wright's case (7) (Partial obstruction by bran in a case of intestinal stenosis).* The author re-

ports a case of partial obstruction of the ileum by bran due to an annular constriction of a benign character. On operation there was found above the stricture a large ball of bran husks which had ulcerated through the bowel and produced a general peritonitis. This patient had had, at intervals, for ten years, mild attacks of cramps and vomiting; but felt well between the attacks. Ten days before the operation she began eating bran for constipation.

*W. C. Alvarez' case (8) (Bran obstruction in narrow adherent loop of the ileum).* Alvarez kindly reports to us in a personal communication of May 8, 1939, the following case: "The woman was about fifty. Some ten years before she had had a hysterectomy, and following this she found that she could not eat roughage. If she did she got an attack of intestinal obstruction which would gradually pass off if she fasted. Shortly before I saw her a physician went over her and told her she must take bran to make her bowels move properly. It apparently did not occur to him that she was constipated because she had to live on such a residueless diet. After taking bran she became obstructed; and, when the symptoms didn't show signs of clearing up, I had to have a surgeon operate in a hurry. We found a knuckle of ileum bound to the stump of the uterus. This segment of bowel had to be resected, and when it was opened the lumen was found to be packed with bran.

"This case shows, of course, not that bran is dangerous for normal people, but that it cannot be used indiscriminately by everyone."

*M. B. Davis' case (9) (bran obstruction: cause not reported).* "Mrs. M. G., aged 50, had had two previous abdominal operations. She had suffered for years from constipation and had at last become firmly addicted to the so-called "pill habit." About a week previous to her trouble she had started to eat bran. On the night of December 2 she retired feeling normal and was awakened at 3 a. m. with severe cramp-like pains in the abdomen, with nausea and vomiting. The patient was diagnosed as having obstruction and was brought to the hospital that day."

"Under spinal anesthesia the abdomen was opened and about twelve inches (30 cm.) from the ileocecal valve in the ileum a complete obstruction was found from a mass of bran about the size of a hen's egg. It was impossible to break this up and to milk it through into the cecum, so intestinal clamps were applied and the mass was removed from the intestines. The patient made an uneventful recovery and was discharged from the hospital in twelve days."

Unfortunately we lack in this report an adequate description of any anatomic abnormality present in this case that might have caused the obstruction or a statement of lack of such predisposing cause. That abnormalities might have been present is rendered very probable by the two previous abdominal operations.

## CONCLUSIONS

1. In a review of the world's literature on bran impaction in the bowel, only four actual cases of this kind could be discovered. In three of these the impaction was preceded by gross intestinal pathology. The fourth case (Davis) is not sufficiently well de-

TABLE I

Cases of intestinal obstruction due to various foods as recorded in literature from 1910 to 1938

Authors	No. of Cases	Age and Sex	Obstructing Material	Location of Obstruction	Predisposing Factors	Treatment	Outcome	Literature
Krauss	1	16 F	Mushroom fiber	Ileum		Bowel resection	Recovered	Zbl. Chirg., 46:2904, 1929
Leisinger	2	54 M	Dried pears (undigested pear size of hen's egg)	Jejunum	No teeth	Resection	Recovered	Schweiz. Med. Wschr., 7:147, 1937
		36 M	Orange (undigested)	Ileum	Postoperative adhesions	Resection	Recovered	
Battle Barker Boswell Drewett	2	42 F	Bran	Sigmoid flexure	Amebic ulcer	Colostomy	Recovered	U. S. Veteran Bureau, Med. Bull., Jan.-Dec., 1928
		30 F	Bran (Diag. made by X-ray) (?)			Enemata	Recovered	
Alvarez	1	F	Bran	Ileum	Postoperative adhesions			Personal
Davis, M. B.	1	50 F	Bran	Ileum	2 previous abdominal op.	Enterostomy	Recovered	J. A. M. A., 97:24, 1931
Wright, C. B.	1	?	Bran	Ileum	Annular constr. of benign char.	Laparotomy no details	?	Minn. Med., 16:73, 1933
Block	1	57 F	Orange	Ileum	No teeth	Enterostomy	Died	Am. J. Med. Sci., 183:356, 1933
Owings	1	58 F	Orange	Ileum	Ventral Hernia Appendectomy	Enterostomy	Recovered	J. A. M. A., 110:365, 1938
Fink	4		Oats Oats Oats Bran (?)	Ileum Ileum Ileum Ileum		Ileostomy Ileostomy Laparotomy Laparotomy	Died Died Died Recovered	Zbl. Chirg., 34:674, 1919
Penkert	2	8 M 39 M	Poppy seeds Poppy seeds, peas, beans	Colon Ileum		Enemata Cecostomy	Recovered Died	Munch. Med. Wschr., 66, 1919
Sil	3	41 F 65 M 59 M	Apple Prune Mushroom fiber	Ileum Jejunum Ileum		Enterostomy Resection Resection	Recovered Recovered Died	Zbl. Chirg., 28:503, 1915
Kaposi	1	?	Fishscales	Colon	Ca of colon flexure	Resection	?	Zbl. Chirg., 17:717, 1914
Marquis	1	?	Cherry stones	Ileum	Stenosis of bowel	Enterostomy	Recovered	Zbl. Chirg., 15:573, 1913
Eichhorst	2	47 F 49 M	909 cherry stones 1010 cherry stones	Ileum-cecum Rectum		Colostomy Manual removal	Died Recovered	Med. Klin., 40:1559, 1910
Beukert	1	56 F	Gooseberry skins and seeds	Rectum		Manual removal	Recovered	Ars. Medici, 1, 1936
Millbaum	6	39 F 52 F 76 M 64 F	Apple pieces Peach piece Apricot piece Baked fruits Baked fruits	Ileum Ileum Ileum Ileum Ileum	Pyosalpinx No teeth Adhesive ribbon and Meckel's Divert.	Enterotomy Enterotomy Laparotomy Laparotomy	Recovered Recovered Died Died	Chirg. J., 1936
Eschaquet	1	11 F	Grapes	?		Conservative	Recovered	Rev. Med. Suisse Rom., 1935
Hugel	1	?	Grapes	Ileum	Appendectomy	Resection	Recovered	Munch. Med. Wschr., 41:1638, 1935
Rohrhirsch	2	10 F 5 ?	Grapes Grapes	Rectum Rectum		Manual removal Manual removal		1934
Moritsch	1	8 F	Dried pears	Rectum		Manual removal		Am. J. Med. Sci., 189, 1935
Frank	1	67 F	Orange	Ileum	No teeth	Enterotomy	Recovered	Presse Med., 97:1977, 1933
Calevenrt	2	?	Locust Locust	Ileum Ileum		Enterotomy Enterotomy	Died Died	Am. J. Med. Sci., 184:85, 1932
Elliot, A. H.	1	36 M	Orange fiber and seeds	Ileum		Laparotomy	Died	Schweiz. Med. Wschr., 14:331, 1931
Heer	1	45 M	Fig	Ileum	Appendectomy 2 yrs. ago	Enterotomy	Recovered	Zbl. Chirg., 20:1619, 1930
Bar	1	36 M	Mushroom fiber	Ileum	Mal. change of retained testicle with chr. ileus	Incisura	Died	Zbl. Chirg., 7:387, 1930
Kruckenber	2	?	Mushroom fiber	Ileum	T.B. stricture ileum	Enterotomy		
		?	Mushroom fiber	Transv. colon	Ca of colon (flexura lienalis)	Colostomy		
Seifert	1	49 F	Sauerkraut	Ileum	Bill Roth for ulcer 5 yrs. ago	Enterotomy	Recovered	Dtsch. Z. Chirg., 224, 1930
Ackmann	1	7 M	Cherry skins and seeds	Ileum		Enterotomy		
Alexander	2	40 M 62 M	Fig Grape	Ileum Jejunum	No teeth Prostatectomy 2 yrs. ago	Enterotomy Enterotomy		
Krecke	1	46 F	Mushroom fiber	Ileum	Enterostomy for stenosis small bowel 5 yrs ago	Laparotomy only	Recovered	Dtsch. Z. Chirg., 215, 1929
Leusden	1	65 M	Gooseberry skins and seeds	Ileum		Laparotomy only	Died	Med. Klin., 24, 1928
Brunzel	3	40 M 50 M 68 M	Beans Cucumbers Cucumbers	Ileum Ileum Ileum		Enterotomy Enemata Laparotomy	Died Recovered Recovered	Dtsch. Z. Chirg., 145, 1928
Chalmers	1	67 M	Fig	Ileum	No teeth. Intest. obstr. 7 yrs. ago	Enterotomy	Recovered	Brit. M. J., 1927

TABLE I (CONTINUED)

Authors	No. of Cases	Age and Sex	Obstructing Material	Location of Obstruction	Predisposing Factors	Treatment	Outcome	Literature
Metre	1	57 F	Potatoes	Ileum		Enterotomy	Died	Zbl. Chirg., 836, 1927
Duhrssen	1	51 M	Mushroom fiber	Ileum		Enterotomy	Recovered	Zbl. Chirg., 1:24, 1927
Riese	3	7 7 7	Mushroom fiber Mushroom fiber Peach	Ileum Ileum Ileum		Ileostomy Ileostomy Ileostomy	Recovered Recovered Recovered	Zbl. Chirg., 1:24, 1927
Wardill	1	66 M	Potatoes	Ileum		Enterotomy		Brit. M. J., 1:56, 1927
Hazelhorst	2	63 F 7 M	Fig Fruit jumps	Ileum Ileum		Enterotomy Enterotomy	Died Recovered	Zbl. Chirg., 25:1664, 1926
Laesel	2	56 M 61 M	Bean Corn kernel	Ileum Cecum		Enterotomy Laparotomy	Recovered Died	
Griffith, W. R.	1	44 M	Orange	Meckel's Divert.		Died before operation		M. J. Australia, 2:556, 1926
Hertz	1	53 M	Fig	Ileum		Enterotomy	Recovered	Bull. Soc. Nat. Chirg., 1925
Goebel	1	44 M	310 cherry stones	Rectum		Manual removal	Recovered	Zbl. Chirg., 1925
Trugshall	1	67 F	Pear	Ileum	No teeth	Enterotomy	Recovered	Acta Chirg. Scand., 57, 1924
Willmoth	4	50 M 20 M 13 F 22 F	Potatoes Grapes Grapes Popcorn	Not known Not known Not known Not known		Enemata Enemata Enemata Enemata	Recovered Recovered Recovered Recovered	Kentucky M. J., 19, 1921
Scheele	2	40 M 32 M	Bean Bean	Ileum Ileum		Enterotomy Enterotomy	Recovered Recovered	Med. Klin., 46:1179, 1920
Walther	3	22 M 42 M 26 M	Kriegs-brot Kriegs-brot Kriegs-brot	Ileum Ileum Ileum		Enemata Enemata Enemata	Recovered Recovered Recovered	Dtsch. Z. Chirg., 1919

Only 6 cases were found in which bran was mentioned. These are italicized in the table. In only 4 of these can bran be considered as actually an obstructing factor. Three of these were preceded by intestinal pathology, and there was probably also such pathology present in the fourth case but the report is inadequate to permit analysis of its nature.

scribed to permit of analysis as to its nature; but predisposing cause was probably present.

2. Bran is obviously not prone to produce intestinal obstruction unless an organic predisposing cause is present.

3. In the presence of intestinal ulceration, stenosis, or disabling adhesions, the administration of bran is contraindicated.

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## Primary Ulcer of the Jejunum\*

By

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and

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**P**ATHOLOGICAL lesions of any kind are relatively infrequent in the jejunum. While primary simple or peptic ulcers are quite common in the stomach and duodenum, and tuberculous, amoebic, typhoid and other types of ulcerations frequently occur in the ileum and colon, they rarely invade the jejunum. This relative immunity of the jejunum has never been adequately explained. After gastro-enterostomy the occurrence of jejunal or gastrojejunal ulcer has been reported as high as 34% and as low as 2%. The factors here are said to be the direct expulsion of acid chyme into a portion of the gut not accustomed to receiving it before neutralization, surgical trauma and individual predisposition. Jejunal ulcer, whether primary or secondary to gastro-enterostomy, offers a serious

prognosis. Primary jejunal ulcer, because of its rarity and the obscurity of its etiology justifies reporting.

Ebeling (1), who made a thorough study of the literature, found only 47 cases of primary jejunal ulcer reported between 1827 and 1932. However, he overlooked 19 cases culled from the foreign literature and reported by Oudard and Jean (2). Between 1932 and 1938 we note the appearance of 9 cases in the American and foreign literature, reported by Nagel (3), Smith (4), Harris (5), Hall (6), Coletti (7), Desjardes and associates (8). Our case here reported brings the total in the literature to date up to 76 cases, covering a period of more than 100 years.

## CASE HISTORY

G. B., a Negro male, age 27 years, entered Provident Hospital on 10-25-34 upon the advice of his family physician after passage of several black bowel movements over a period of three days. No pain occurred during this

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period, although at intervals during the past few years he had received treatment for "indigestion." Within 12 hours after entrance the patient had a severe attack of abdominal pain, mostly epigastric, accompanied by a sharp elevation of temperature to 104.5. He became nauseated and vomited bright red blood. This was followed shortly by a black soft bowel movement.

*Physical Examination* revealed a weak, pale, anxious patient with rapid pulse. The abdomen was somewhat tender but not rigid. A diagnosis of bleeding peptic ulcer was made. The lesion was considered to be penetrating because of the associated acute pain. A transfusion of 500 cc. of blood and 2500 cc. of Ringer's solution subcutaneously was given preparatory to laparotomy.

*Laboratory Findings* showed a Hb of 75% on entrance which fell to 48% the first day. The red blood cell count was 3,590,000 just before operation. The hemoglobin at that time was 28%. The stools were black and tarry and gave a four plus benzidine reaction. The blood Wassermann and Kahn tests and urinalysis were negative.

Laparotomy performed by one of us (U.G.D.) disclosed a normal stomach and duodenum, externally. Gastrotomy revealed no defects of the mucosa and no free blood in the gastric content. Blood in the intestines could be seen through the translucent wall of the ileum as a purplish discoloration. This appearance ended rather abruptly in the lower portion of the jejunum. Six or seven cm. beyond this point an indurated area of irregular outline could be palpated. On opening the jejunum an annular defect of the mucosa was found about 18 cm. below the ligament of Treitz measuring about 1 x 6 cm. and bleeding actively. Resection and end to end anastomosis were performed. The bowel was examined before and after resection for similar defects elsewhere but none were found.

There was complete recovery and on the date of discharge, fifteen days after entrance, the patient had a hemoglobin of 70%, red blood cell count of 3,500,000 and was without symptoms.

*Follow Up:* One year and two months later the patient was well and working at a steel mill.

*Etiology and Pathogenesis.* Any discussion of the etiology and pathogenesis of primary jejunal ulcer opens up the entire question of etiology and pathogenesis of primary chronic ulcer at any location in the gastro-intestinal tract. As is well known, the overwhelming majority of chronic peptic ulcers occur in the distal portion of the stomach and the immediately adjacent duodenal bulb, the receptacle for the acid chyme before it is neutralized by the alkaline intestinal juices. It is maintained perhaps by the preponderance of evidence that this acid chyme is an absolutely essential factor in the production of peptic ulcer and probably the most successful therapy, medical and surgical is explained on this basis. In this regard it is interesting that primary jejunal ulcers originate in an alkaline medium. They therefore can not be regarded as of peptic origin. However, true peptic ulcers do occasionally occur in Meckel's Diverticula (9) and in the esophagus where dystopic rests of gastric mucosa and evidence of secretion of acid have been demonstrated. Tissue similar to acid bearing gastric mucosa has also been observed in the intestines by Nicholson (10), Sweet (11), Stone (12) and others. In these cases however the lower small intestines were involved and not the jejunum. None of the cases of primary jejunal ulcers in the literature, nor did our case, show evidence of aberrant gastric mucosa. It seems plausible that if acid chyme is the principle etiological agent in chronic gastric and duodenal ulcer that tryptic digestion under certain conditions may become the principal cause of chronic primary ulcer

of the jejunum in a "susceptible" patient. Volini and associates (13) have found duodenal ulcers in Mann-Williamson dogs in which the duodenum is safely excluded from entrance of acid gastric juice. While autodigestion may be the principal factor, there are other factors which must be considered in the pathogenesis of primary chronic ulcers of the upper gastrointestinal tract. There is the question of why one patient with a fairly high gastric acidity curve may never have an ulcer and others with a fairly low acidity curve may develop ulcer. It is evident that some additional factor or factors must be necessary to make possible autodigestion in a given case.

It may be that infection from distant foci, vasomotor (14) spasm or primary jejunitis may precede primary jejunal ulcer and have the same etiological relationship as they do in gastric and duodenal ulcers. Why these predisposing conditions occur so rarely in the jejunum is still a matter of conjecture.

*Pathology.* The great majority of the ulcers reported in the literature were of circular punched out configuration, the others being annular. The majority

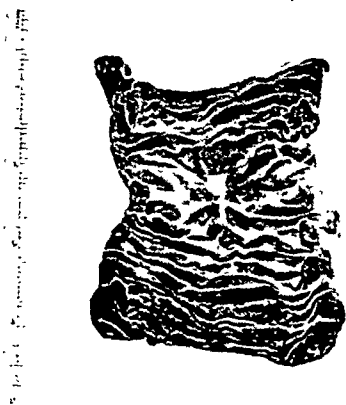


Fig. 1. Section of jejunum showing annular ulcer with indurated edges parallel to Kyrkring folds. (Two pieces have been excised for histological study).

were recorded as chronic, the edges were sometimes undermined. There was usually some thickening and induration of the walls and floor of the ulcer. In one case the lesion extended through the submucosa. Most of the cases presented single ulcers but some were multiple. Several were associated with gastric and duodenal ulcers. The microscopic picture was essentially that of moderate infiltration with lymphocytes and plasma cells and proliferation of connective tissue.

In our case the gross configuration was annular (see Fig. 1) and of irregular outline with some induration of the edges and actively bleeding at the time of the operation. There was nothing grossly about the ulcer or in its vicinity which simulated aberrant gastric tissue. There was no foreign body or gross evidence of malignancy, tuberculosis or other specific disease at the site of the lesion or elsewhere in the abdomen. The regional lymph glands were of normal size and consistency. Microscopically there was no endarteritis or endophlebitis or endothelial cell proliferation suggestive of syphilis. A Levaditi stain failed

to demonstrate the spirocheta pallida and there was no evidence of tubercles or tuberculous granulation tissue. The section through the base and edges of the ulcer showed no dystopic gastric tissue. It was moderately infiltrated with round cells and considerable connective tissue proliferation had occurred.

**Symptomatology:** The symptoms of several of these cases simulated rather closely those of gastric and duodenal ulcer. At least five of the cases in the literature of jejunal ulcer unassociated with gastric or duodenal ulcers had pain one to three hours after meals and late at night which was relieved by alkali. Many others had all gradations of dyspeptic symptoms without the classical periodicity and rhythmicity of gastric and duodenal ulcer. These included epigastric burning or gnawing at irregular intervals, flatulence, nausea, occasional vomiting, waterbrash. Melena was recorded in only two of the cases in the literature but was the predominating symptom in our case. The great majority of the cases, 49 out of 57 terminated in spontaneous perforation. This very high incidence of complications and particularly perforation as compared with similar complications in gastric and duodenal ulcers remains to be explained. Many cases had attacks of pain for weeks and months and spontaneous remissions and recurrences as, for example, the cases reported by Walton (15), and others. Most of the

cases where gastric acidity tests were made showed a hypochlorhydria.

### SUMMARY

1. Primary jejunal ulcer is reported quite infrequently in the medical literature.

2. A proven case of Primary jejunal ulcer of the "Simple" type with successful surgical removal is here reported.

3. There are no pathognomonic signs or symptoms of the lesion. Absorption of blood within the small intestine is often associated with disproportionately high temperature, as in the case reported.

4. The occasional occurrence of primary chronic ulcer of the jejunum must be kept in mind, when there is a clinical impression of ulcer and gastro-duodenal X-ray and gastroscopic findings are negative.

5. In case of excruciating pain and abdominal signs of ruptured viscus in the upper half of the abdomen, the occasional occurrence of ruptured primary jejunal ulcer must be remembered.

6. In cases of hemorrhage from the upper gastrointestinal tract, conservative management should be tempered with careful watchfulness and due regard for the fact that the occasional bleeding primary jejunal ulcer has an overwhelming tendency to rupture and is therefore probably best handled surgically.

**Note:** For the privilege of this case report we are indebted to Dr. Audley F. Connor, Provident Hospital.

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## A Study of Liver Function in Experimental "Peptic" Ulcer\*

By

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**EVIDENCE** regarding the possible etiologic relationship between "peptic" ulcer and liver dysfunction has been presented in a number of clinical articles. Most of this literature has been reviewed by Jergesen and Simonds (1). The conditions under which a spontaneously occurring "peptic" ulcer may be associated with liver dysfunction or impairment in the dog have been summarized by Ivy, Schrager and Morgan (2). In dogs operated on according to the Mann-Williamson procedure, in which a gastrojejunostomy is performed and the alkaline digestive juices are drained into the lower ileum, jejunal ulcer occurs in about 98 per cent of animals within 4 months. Ivy and Fauley (3) were unable to detect significant histologic changes in the liver of such animals. They examined sections of the liver histologically before

and after the development of ulcer in over 20 such dogs. This present work was undertaken to ascertain if the development of post-operative jejunal ulcer is associated with a detectable disturbance of liver function.

### METHODS

The following tests were made before the operation and at various intervals after the operation until the animal died or was sacrificed: the Van den Bergh, quantitative bilirubin, the blood lipase according to Crandall and Cherry (4) and the bromsulphthalein test according to Rosenthal and White (5). All tests were carried out during the same day and, in many cases, checked the following day. In the case of the bromsulphthalein test 4.0 mg. per kilo body weight were injected and in the control tests the dye had completely cleared in 30 minutes. A total of 47 dogs were studied, 31 with the Mann-Williamson operation and 16 that received cinchophen. The presence of ulcer was diag-

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nosed by the presence of tarry stools or in some instances by exploratory operation.

## RESULTS

The essential observations will be summarized. Before operation all the dogs gave normal values for the various liver function tests.

Group I. Seventeen dogs were operated on. All were placed on mucin-alkali therapy. Two developed a bilirubinemia, amounting to from 3.9 to 4.1 mg., just prior to the perforation of the ulcer. In these two animals the blood lipase values were elevated from two to three times normal. Bromsulphthalein retention was present, the retention at 30 minutes being 15 and 6 per cent. In eleven of the thirteen dogs which developed ulcer, a positive blood lipase (more than 0.2 cc. of N 20 NaOH) and a positive bromsulphthalein test was obtained. These positive tests were obtained shortly before the ulcer perforated and not coincident with its development. Thus, bromsulphthalein retention and a rise in blood lipase was much more frequent than bilirubinemia. In three of the eleven, the two tests gradually increased in the degree of positiveness until perforation; in the others the tests became positive shortly before perforation. In one dog in which healing of the ulcer was secured and proven by exploration, the bilirubinemia amounted to 0.25 mg., the blood lipase value to 1.0 cc. of N/10 NaOH, and the dye retention to 10 per cent at 30 minutes during the active stage of the ulcer; after healing these values returned to the normal values for this dog. *These results indicate that when the dog is placed under much stress as the result of hemorrhage from an ulcer and especially shortly before perforation, liver function is frequently disturbed sufficiently to be detected by the functional tests used. The liver is not detectably disturbed prior to the development of ulcer.*

Group II. Fourteen dogs were studied in this group. A fundusectomy was first performed and then several weeks later a Mann-Williamson operation was performed. The fundusectomy did not affect liver function. Ten of these dogs did not develop ulcer because of the fundusectomy and special diet they received (6). These dogs showed no significant change in liver function, which shows that the operation *per se* has no effect on liver function as revealed by the tests used. Three of the four dogs that developed ulcer, but which did not receive the special diet (6), showed a slight elevation in dye retention (3 to 5 per cent) and in blood lipase (.3 to .6 cc), and one a bilirubinemia of 0.25 mg., shortly before perforation. The results on the ten dogs which did not develop ulcer constitute an excellent "long-time" control series and show that the operations *per se* did not affect the liver according to the tests used.

Group III. Cinchophen. Five dogs were given cinchophen in doses of 100 mg. per kilo intraperitoneally for two days. One or two days later the results of the liver function tests showed no significant change.

The remaining 11 dogs were given 100 mg. cinchophen (the cinchophen marketed prior to 1936 which had a light brown color) per kilo orally in starch daily. These dogs also received orally 30 gm. of gastric mucin twice daily. All these dogs except one survived for 90 days on the cinchophen without developing

ulcer. The one that died on the 60th day showed an increased dye retention, blood lipase value, and a bilirubinemia the day before death. In the remainder, which were chloroformed on the 90th day, blood lipase was increased in 6, dye retention was increased in 4, and bilirubinemia was present in 1 after 60 to 90 days of cinchophen. These animals were those which lost the most weight. *Thus, evidence of liver damage was obtained by means of liver function tests in the absence of the development of ulcer.* Cinchophen is known to cause histologic damage of the liver when given without gastric mucin (7).

## DISCUSSION

It cannot be concluded from our results on the Mann-Williamson dogs that the liver plays no rôle in the post-operative development of jejunal ulcers. This is because much hepatic insufficiency must exist before the liver function tests used can detect it. The changes in liver function observed were terminal in nature or occurred when the body was placed under considerable strain by the embarrassment of hemorrhage or threatened perforation. The results on cinchophen are rather clear-cut in showing that the liver can be considerably damaged, at least in some respects, without ulcer resulting.

## SUMMARY AND CONCLUSIONS

1. The quantitative bilirubin test and the blood lipase and bromsulphthalein retention determinations for liver function were applied to 31 dogs on which the Mann-Williamson operation was performed for the production of post-operative jejunal ulcer. It was found that the operation *per se* does not cause a detectable disturbance of liver function according to the tests used. When the body is much embarrassed by a loss of blood or threatened perforation in consequence of the development of an ulcer, liver function is deranged in some but not all cases. The liver was not detectably disturbed prior to the development of the ulcer.

2. The same tests were applied to 11 dogs which received daily 100 mg. of cinchophen, made prior to 1936, for 90 days along with 60 gm. of gastric mucin. None of the dogs developed ulcer, but evidence of liver damage was observed in six, which shows that liver damage may be produced by cinchophen without causing an ulcer.

3. These observations indicate that if liver injury has anything to do with the etiology of experimental ulcer in the dog, it must be a fairly specific type of injury.

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# Relation of Blood CO<sub>2</sub> and Dehydration to Gastric Acidity

By

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OF the various causes which have been ascribed to peptic ulcer, gastric acidity has been by far the most important and tangible. Practically all active therapy quite logically has been directed against the acid factor. This has largely taken the form of the administration of countless different alkalies.

The benefit derived from the ingestion of the alkalies is produced by their ability to neutralize the hydrochloric acid of the stomach. In no way do they lessen the production of acid. In fact there is strongly suggestive evidence that some of the bases, such as sodium bicarbonate, actually have a tendency to increase the acid secretion of the stomach (1, 2).

The universal use of alkalies to combat gastric acidity speaks for itself. It is the accepted means of treating peptic ulcer. Nevertheless, this form of therapy does not strike at the root of the problem. It does not reduce the amount of acid formed. It merely neutralizes that which has been formed.

Numerous attempts have been made to decrease the actual production of gastric acid. These may be placed in three groups—(1) those directed toward an interruption or alteration of the gastric nerve supply, (2) radiation to the gastric mucosa to decrease its function in producing acid and (3) analysis and attempted alterations in the blood chemistry to prevent excessive acid formation.

It is toward this third group that our attention has been directed. Interest has been centered on the alleged correlation between the blood CO<sub>2</sub> and the gastric acidity (3, 4, 5). If this parallel is true, it is of therapeutic as well as academic value. It might be possible to drop the blood CO<sub>2</sub> artificially to a mild acidosis. By so doing acid values might be lowered likewise to a level which would be beneficial.

To investigate this possibility the following experiments were undertaken:

## METHODS

Pavlov pouches were produced on five healthy mongrel dogs. Acid excoriation and infection about the pouch stoma prevented the use of three dogs. The other two dogs maintained their weight very well during the period of the tests and showed no ill effects from the gastric fluid loss. Large mushroom catheters were inserted into the pouches. These facilitated collecting the gastric juice and also prevented excessive skin excoriation. One dog weighed 16.5 kilograms at the start of the experiments, the other weighed 16.6 kilograms. At the conclusion of the tests two months later neither dog had changed more than one kilogram in weight.

Animals were observed for several weeks after operation. The gastric secretion following test meals was

recorded. Tests were started only after a more or less constant level of gastric secretion had been reached. Titration for free hydrochloric acid was carried out using Töpfer's reagent while phenolphthalein was used for the total acid titration.

The animals were fed on a milk and meat ration at 1:00 p.m. each day. Histamine phosphate, .5 mg., was given subcutaneously at the same time of feeding for additional stimulus to secretion. The gastric secretion from the Pavlov pouch was collected in a flask for a two-hour period following this procedure. It was carefully measured and titrated.

Plasma blood CO<sub>2</sub>, blood chloride and total non-protein nitrogen determinations were made periodically as seemed indicated.

Various salts were given to the dogs in capsules to determine their effect on the gastric secretion of the Pavlov pouch. These salts consisted of sodium bicarbonate, sodium chloride and ammonium chloride. Any effect which the salts might produce would be a systemic effect since the pouch was entirely separated from the remaining portion of the stomach.

The feeding of sodium bicarbonate and also sodium chloride has been carried out by others. We have found no report on the feeding of ammonium chloride. The purpose of this salt was to produce varying degrees of acidosis. By so doing it was hoped that the pouch gastric secretions would follow the blood CO<sub>2</sub> in a downward course. Whether this would be of any therapeutic value is quite another matter.

In all, some 356 acid determinations were made on the Pavlov pouch secretions of the two dogs. These followed the meat and histamine stimulation previously noted. The amount of pouch secretion, the free, total and combined hydrochloric acid were carefully tabulated.

## RESULTS

Since we were unable to demonstrate any correlation between the blood CO<sub>2</sub> and the acid produced by the Pavlov pouch, there seems to be no reason for detailing the protocols. A graphic representation of this phase may be seen by reference to Fig. 1. Here it is seen that on the thirty-third day of the run on Dog 4, ammonium chloride was given in capsules, 12 grams each day. This amount caused a very definite lowering of the blood CO<sub>2</sub> (35.3 volumes per cent) but caused no lowering of the quantity or acidity of the pouch secretion. In fact there was a very definite rise in this secretion. The ammonium chloride was then increased to 24 grams each day. It is seen that this caused the CO<sub>2</sub> to fall to 26 volumes per cent with still a very high acid output.

It certainly would be inadvisable clinically to lower the blood CO<sub>2</sub> beyond the above figure; therefore,

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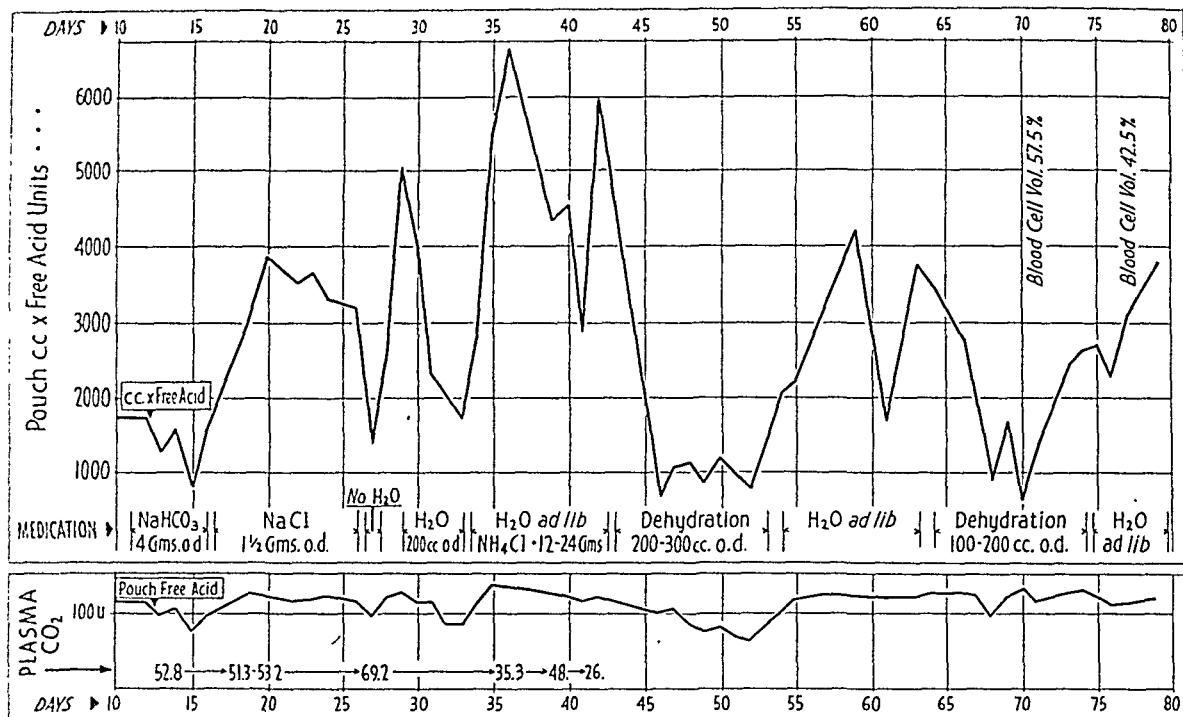


Fig. 1. Graphical representation of acid production from Pavlov pouch in Dog 4, weight 16.6 K. The lower solid line indicates the pouch free acid for a two-hour specimen following meat diet and histamine stimulation. It is seen that the "clinical units" of free acidity is remarkably constant under the various forms of medication used. This is in sharp contrast with the upper dotted line which indicates the volume of pouch secretion times the free acid units. The wide variation of this effective free acid is of significance since it more nearly pictures the true state of acid production and control. As indicated on the graph the plasma  $\text{CO}_2$  was dropped to 26 volumes per cent by feeding ammonium chloride. Even this degree of acidosis caused no reduction in pouch acid secretion. It should be noticed that dehydration of the animal invariably resulted in a drop in the total secretion. The degree of dehydration necessary to produce this reduction is quite within clinical limits as indicated by blood cell volumes at the right of the graph.

there seemed little point in carrying this further, especially since the pouch acid values were increased rather than decreased.

It is concluded then that acidosis in dogs produced by feeding ammonium chloride caused no reduction in the quantity or acidity of a Pavlov pouch secretion. This in part substantiates the work of Kiefer (6) who doubts that any artificial shifts of the blood electrolytes will materially change the gastric secretion.

In our experiments a very definite increase in this secretion was noted with the administration of ammonium chloride. This was attributed to a coincident increased water intake as a result of the ingested salt. It will be noted (Fig. 1) that the feeding of sodium chloride caused a like increase in the pouch secretion.

Combined and total pouch acidity followed practically identical ratios with the free acidity. They therefore are omitted from the graph for clarity.

#### DEHYDRATION

Acidity of the gastric secretion is too frequently considered in terms of "clinical units." This does not take into consideration the amount of effective acid. Thus a clinical test meal may show a very high free acidity in "clinical units" but neglects to indicate the amount of acid secreted. This is important since a small amount of highly acid secretion may be easily handled by the normal diet or by small amounts of

alkali. On the other hand such means would be quite ineffective in dealing with a patient having the same degree of acidity but with an excessive secretion.

In the present study this factor has been taken into consideration. The units of free acid have been multiplied by the cc. of secretion for the particular test period. This is indicated in the upper graph of Fig. 1. When dealing with gastric pouch experiments this gives an accurate picture of the acid situation.

A glance at this plotted curve indicates a wide fluctuation in the quantity of pouch secretion while the acidity of this secretion (lower curve) remains remarkably constant. There is, however, one constant in the "cc. x free acid" curve which cannot escape attention. This is the sharp drop which it manifests every time the animal was dehydrated. Liquid was never withheld for longer periods than 24 hours. It was, however, limited to daily amounts of 100-300 cc. for as long as ten days at a time. During these periods the animals remained in excellent health. They were, of course, quite willing to drink more water than was allotted. However, they evidenced no hardship even though many of the periods included some very hot summer days. On each occasion when water and milk were again allowed as desired, the amount of pouch secretion rose to a high level.

The observation of a lowered secretion with dehydration is by no means new or original. This fact

has been pointed out for some time by physiologists. A number of years ago Sutherland (7) emphasized the dependency of gastric secretion upon the available water content of the body.

The clinical possibility of dehydration therapy naturally suggested itself. Could a patient with peptic ulcer be controlled in a partially dehydrated state? We felt quite sure from our experimental work that he *could*; but *would* he? Would the thirst and craving for water be too much of a burden for the average will power?

At the present time we have had a small experience in treating peptic ulcers by dehydration. The results of this will be the subject of a future communication. It may be said, however, that dehydration of the ulcer patient is not without danger and there is usually considerable discomfort from thirst. The amount of gastric juice produced by these patients was markedly diminished but their free acid values remained practically the same.

### CONCLUSIONS

(1) An attempt was made in dogs to determine a correlation between the plasma  $\text{CO}_2$  and the gastric acidity. No such correlation could be demonstrated by the methods used.

(2) The plasma  $\text{CO}_2$  was lowered to 26 volumes

per cent by feeding ammonium chloride. This caused no decrease in the free acidity of Pavlov pouches. Concurrent with the administration of this salt there was a great increase in the pouch secretion attributed to a coincidental water intake from thirst produced by salt ingestion.

(3) The importance of evaluating the total amount of effective free acid is emphasized rather than considering only free acid "clinical units."

(4) Dehydration was quite effective in reducing the amount of pouch secretion but caused only a little change in the free acid. Dogs can be maintained for days on such a dehydration regime without apparent distress or harm.

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## The Early Diagnosis of Cancer of the Pancreas\*

By

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NOW that surgery offers hope to patients with cancer of the pancreas (1, 2, 3), it is imperative to recognize its earliest manifestations. When jaundice is one of the presenting symptoms, the problem is somewhat simplified because, once the medical causes of this symptom have been eliminated, exploratory surgery is indicated. Unfortunately, however, in a considerable proportion of cases jaundice may be a comparatively late symptom. In fact, in 40 per cent of the cases seen at the Peter Bent Brigham Hospital, jaundice has appeared as late as several weeks or months after the onset of the illness. It is to a consideration of the symptoms which may lead to the diagnosis before the onset of jaundice that the present paper is directed.

Painless jaundice is often erroneously stated to be the classical picture of cancer of the pancreas. Actually, in a majority of the cases, pain is a prominent symptom (4, 5, 6, 7, 8), and, in certain cases, it may furnish an important diagnostic clue before the onset of jaundice. This is particularly true when the neoplasm extends into the body of the pancreas (9, 10). The character of the pain merits further consideration. In general there are three types (8, 10). One is a steady, boring ache in the epigastrium extending into the back. Another occurs in severe paroxysms, arising in the epigastrium or either hypochondrium, and radiating to the back, flanks, chest, umbilicus, or lower abdomen. A third type is a colicky

cramp in the right upper quadrant, appearing at the time of onset of jaundice and then subsiding. It is common for more than one type of pain to occur in the same patient. Thus, at first paroxysmal, the pain may later become constant and boring with acute exacerbations. Persistent upper abdominal pain extending into the back, worse at night or when the patient is lying down, is particularly suggestive (11). As a rule the pains are not closely related to meals, but epigastric distress and an unbearable sense of fullness of the stomach are common associated complaints. Frequently, exercise or jolting, as riding in a car, tends to exaggerate the pain.

Loss of weight is an important and characteristic symptom. It has been said that in no other disease is there such rapid cachexia. Thirty or forty pounds may be lost in a few weeks. This is often quite out of proportion to the size of the tumor or the diminished intake of food.

The importance of nervous symptoms as an early manifestation of cancer of the pancreas was first pointed out by Yaskin (12). He reported four cases, in three of which the diagnosis was established at operation. Prominent complaints were depression, anxiety, insomnia, and weight loss. Despite the later development of abdominal pain, diagnoses of some type of neurosis were made after careful study by competent internists. Only later, when jaundice or an abdominal mass appeared, was the real cause of the symptoms suspected. Similar observations have been made by others. Scholz and Pfeiffer (13) noted ex-

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treme nervousness as an outstanding complaint of one of two patients with cancer of the tail of the pancreas.

The Case Records of the Massachusetts General Hospital (14) contain a striking illustration of the symptoms described above. A male, aged 39, entered that hospital complaining of abdominal pain, headache, irritability and nervousness. The pain radiated to the back, was particularly severe at night, and was exaggerated by exercise. The patient lost weight rapidly. Physical examination and laboratory and roentgen studies were interpreted as negative. Despite the severity and continuance of the pain, a diagnosis of a functional disorder was made on two separate admissions to the hospital. At a third admission, approximately six months after the onset of the illness, jaundice developed and eventually the true nature of the disease was recognized. In a discussion of the post mortem findings, Dr. Tracy Mallory recalled similar instances in which diagnoses of psychoneurosis had been made in the early stages of cancer of the pancreas.

The following case also emphasizes the necessity of paying due regard to the symptom complex described above if serious mistakes are to be avoided.

A 35 year old salesman entered the Peter Bent Brigham Hospital complaining of severe abdominal pain, constipation, and loss of weight of three months duration. The present illness was initiated by an attack of severe cramp-like midabdominal pain which radiated into both flanks. There was no nausea or vomiting, but since the onset the patient had had a sense of abdominal fullness which caused him to avoid heavy meals. The pain was steady and aching in character, with occasional severe paroxysms. On one occasion it was so severe that he lost consciousness. It was worse at night and frequently awakened him from sleep. In the course of three months he lost 40 pounds in weight and, for the first time in his life, suffered from constipation which was relieved only by frequent catharsis.

Prior to this illness the patient had been in good health. He occasionally suffered from migraine and in the past had had several attacks of mild painless jaundice. Recently he had had financial reverses which upset him greatly. He appeared introspective and had a great dread of being thought neurotic.

Physical examination at the time of admission was negative. There was a slight fever—not over 100° F. Laboratory studies disclosed a glycosuria and a diabetic type of glucose tolerance curve. The erythrocyte count was 4,800,000 per cu. mm. The leucocyte count was 8500 per cu. mm. Hinton and Wasserman tests were negative. Examinations of the stools were negative. A tentative diagnosis of biliary disease or low grade intestinal obstruction was made. These were excluded by a roentgen examination of the biliary and gastro-intestinal tracts. It

was then felt that the patient was unconsciously exaggerating his symptoms. He himself began to feel that his pain was neurotic in origin. Small doses of insulin brought about a temporary alleviation of the pain, but after twenty-four hours it returned with greater severity. The patient was discharged after a period of observation of three weeks duration. The final diagnosis was diabetes mellitus and intestinal neurosis.

The pain continued unabated and one month later jaundice developed. Death occurred six months after the onset of the disease. Post mortem examination at another hospital disclosed a cancer of the head of the pancreas with metastases to the liver, lungs and bones.

Certain rare complaints, which should lead one to suspect cancer of the pancreas, are an unexplained and intractable diarrhea (6, 15), persistent nausea unrelated to meals (8, 16), or a peculiarly unbearable type of epigastric distress (17). Although not frequently seen, these are unusual complaints which, in lieu of an adequate explanation, may suggest the diagnosis to the keen observer. If associated with persistent abdominal pain and weight loss, without roentgenological evidence of a lesion in the gastro-intestinal tract, surgical exploration rather than expectant treatment is indicated.

Usually the X-ray examination is only of negative value in cancer of the pancreas, but there are three positive findings which should be looked for and which, if present, are of diagnostic import. These are a widening of the duodenal loop, pressure defects of the duodenum or pylorus, and, in cancer of the tail of the pancreas, pressure defects of the greater curvature of the stomach (13). Such changes may be overlooked or recorded without their significance being realized until after the disease has progressed to a fatal issue (14).

In summary, it may be said that cancer of the pancreas is an operable lesion when recognized early. Before the onset of jaundice, it is particularly difficult to establish the diagnosis. Important symptoms are persistent, inexplicable abdominal pain, radiating to the back, worse at night or when the patient is lying down, and weight loss of an unusually rapid nature. Unexplained, intractable diarrhea, persistent nausea unrelated to meals, or a peculiarly unbearable type of epigastric distress are uncommon complaints which, however, may suggest the diagnosis to the keen observer. The X-ray examination merits careful study as it may contribute positive as well as negative evidence. Under such circumstances as are illustrated in the above case report, exploratory surgery rather than expectant treatment must be employed if favorable results are to be expected.

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# The Effect of Enteral Absorption of Fluids on the Recovery of the Blood Pressure after Severe Hemorrhage\*

By

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IN 1938 some studies were reported (Van Liere, Northup and Sleeth) (1) on the effects of acute hemorrhage on absorption from the small intestine. It was found that barbitalized dogs which had been bled 3.2 per cent of their body weight absorbed less distilled water from the small intestine than did the control animals. The hemorrhaged animals, however, absorbed more isotonic chloride solution than did the controls. The absorption of isotonic glucose solution from the intestine was unaffected by hemorrhage.

The question arose whether the increased absorption of sodium chloride solution actually assisted the systemic blood pressure to regain its normal level. If this were true, it might be logical to suppose that the increased blood pressure in turn favorably affected absorption from the intestine; this chain of events

embodied the jejunum and ileum. This loop of intestine was washed out with isotonic glucose solution. Both ends of the loop were tied off and the intestine replaced into the abdominal cavity.

The animals were then bled 3.2 per cent of their body weight. The blood pressure tracings were recorded during the period of hemorrhage and one and one-half hours subsequently.

Immediately after the animal had sustained the hemorrhage, the effect on absorption from the small intestine of distilled water, physiological saline solution and dog's serum was studied on the blood pressure. Each substance was studied separately. The intestinal loop was filled by means of a large syringe equipped with a 13 gauge needle. Care was taken to

TABLE I

*The effect of enteral absorption of fluids on the recovery of the blood pressure after severe hemorrhage*

Substance Absorbed	B.P. Before Hemorrhage	Low Point Reached After Hemorrhage	B.P. at Time of Injection of Fluid Into Gut	Maximum B.P. During Absorption	Time After Injection Maximum B.P. Was Reached	B.P. 90 Min. After Injection
	mm. Hg.	mm. Hg.	mm. Hg.	mm. Hg.	Min.	mm. Hg.
Control (10 dogs)	143	27	57	110	63	102
Dog Serum (10 dogs)	140	30	58	122	51	117
Normal Saline (10 dogs)	143	30	50	113	52	103
Distilled Water (8 dogs)	137	30	57	104	•	•

\*Only part of series continued for 90 minutes.

would be distinctly advantageous to the animal organism.

It was thought worth while to study the effects of absorption of various substances from the small intestine on the recovery of blood pressure after severe hemorrhage.

## METHODS

Dogs which had been given barbital intravenously (220 mg. per kilo) were used in this work. Blood pressure tracings from the carotid artery were obtained. The small intestines were exposed by a mid-line incision. A loop was prepared which virtually

avoid undue distension. The substance was left in the gut for one and one-half hours.

Ten animals were used when physiological salt solution and dog's serum was studied, but only 8 were used when distilled water was placed into the intestine. A control group of ten animals was also used. These control animals were treated like the experimental groups, except that nothing was placed in the intestine.

## RESULTS

Table I and the accompanying chart show the results obtained. It will be seen that the absorption of normal saline solution did not materially aid in the restoration of blood pressure. The blood pressure in the control dogs rose to a maximum as quickly and

\*From the Department of Physiology, University of West Virginia. Aided by a Grant of the Ella Sachs Plotz Foundation. Submitted August 11, 1939.



was as high at the end of 90 minutes after the hemorrhage.

The group of animals which had had dog serum placed in the intestine showed a somewhat higher blood pressure at the end of 90 minutes than did the controls. The maximum blood pressure reached during the period of observation also showed a somewhat higher figure. These figures, however, when statistically analyzed were not significant. The time after in-

of serum 64.1 per cent of it was absorbed within a period of 90 minutes. The percentage replacement of the blood by the serum was 30.8 per cent.

The study of the absorption of distilled water from the intestine was probably of no practical significance since distilled water is not a normal constituent of the small intestine. Water normally is ingested orally and by the time it reaches the lower part of the ileum where most of the absorption of water takes place it probably is an isotonic solution. Water normally ingested then would be absorbed from the intestine in the form of an isotonic solution.

In this discussion it must be remembered that we are dealing only with immediate effects on the blood pressure. The body recovering from a severe hemorrhage calls upon its water reservoirs such as that stored in the subcutaneous tissues and the muscles. Indeed it is considered that after a severe hemorrhage about one-half of the water supplied to the blood is furnished by the skin and the remainder by the muscles (3). The mobilization of water from these reservoirs doubtless is a gradual process. The work reported here is not intended to minimize the importance of administering fluids following a hemorrhage, for it is obvious that the depleted water reservoirs must be replenished. The work reported here, however, does show that fluids present in the small intestine are of no immediate aid in the restoration of blood pressure after severe hemorrhage.

Lastly, it must be pointed out that a blood loss in a dog of 3.2 per cent of its body weight constitutes a very severe hemorrhage; about 20 per cent of the dogs died.

## SUMMARY AND CONCLUSIONS

Dogs under barbital anesthesia were bled 3.2 per cent of their body weight. Blood pressure tracings from the carotid artery were recorded for one and one-half hours subsequently. The effect of absorption from the intestine of water, physiological salt solution and dog serum was studied on the restoration of the blood pressure. It was found that the absorption of normal saline solution or water did not aid in the recovery of the blood pressure. Animals absorbing dog serum showed a somewhat higher blood pressure than the controls. This difference was not statistically significant. Amounts of the various fluids placed in the intestine were absorbed which if given intravenously would be expected to be of distinct aid in restoring the blood pressure.

It is concluded that oral administration of fluids during the acute phase of recovery from severe hemorrhage is not of material assistance to the organism as far as the immediate restoration of blood pressure is concerned.

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TABLE II

*Absorption of dog's serum from small intestine*

Animal Number	Amt. of Blood Withdrawn	Amt. of Serum Injected	Amt. of Serum Absorbed at End of 90 min.	Percentage of Serum Absorbed
	cc.	cc.	cc.	Per Cent
1	415	200	156	78.0
2.	585	270	156	57.4
3.	260	100	71	71.0
4	370	167	107	64.1
5.	380	200	76	38.0
6.	230	150	122	81.3
7.	165	200	112	56.0
8.	420	130	93	71.6
9.	200	150	88	58.7
10.	270	180	117	65.0
Avg.	356.6	175.0	110.0	61.1

jection when the maximum blood pressure was reached was about the same as that when physiological salt solution was absorbed. Table II shows the absorption of dog's serum from the small intestine.

## DISCUSSION

The experiments indicate that enteral absorption of distilled water, physiological salt solution or dog's serum have but little if any effect on the immediate recovery of the blood pressure after severe hemorrhage. Amounts of the various fluids were absorbed, which if they had been given intravenously after a severe hemorrhage, would have aided in restoring the blood pressure to its normal level.

At the end of 90 minutes no distilled water was left in the intestine; former work (2) has shown that practically all the water is absorbed from the small intestine within a period of about 40 minutes. In the majority of the dogs all the saline had been absorbed at the end of 90 minutes. In the ten animals 88.6 per cent of the normal saline solution was absorbed. The replacement of blood by the absorbed saline was 46.2 per cent. When the absorption of dog's serum from the intestine was studied, the average amount of blood withdrawn was 356 cc. and the average amount of serum injected was 175 cc. or approximately one-half of the total blood volume withdrawn. Of this amount

# Gastric Analyses and Gastric Symptoms in Diabetes Insipidus\*

By

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IN observing a group of 27 patients with diabetes insipidus of idiopathic origin during the past six years, indefinite gastric symptoms such as nausea, vomiting, heart burn, retching and poor appetite appeared to be a common complaint especially in the morning when no pituitrin had been administered for several days. Most patients with this disease have had varying amounts of abdominal cramps following treatment with pituitrin given by injection. This type of symptom, however, has largely disappeared since so many of the patients with diabetes insipidus now take the pituitrin intranasally.

Because of these complaints a study was made to determine whether there were any unusual changes in

of 8 per cent alcohol. The test was made on one morning after the patient had omitted pituitrin for several days. It was repeated on another morning after the patient had been treated with pituitrin for a few days and in this test 1 cc. of pituitrin of obstetrical strength was injected intramuscularly immediately after the fasting specimen was obtained. The volume of gastric juice and the free and total acid were quantitated in each specimen. Then, the proteolytic effect of the gastric juice was determined by adding pieces of egg albumin, which were coagulated by heating, to each specimen of gastric juice. These were incubated at 37° C. and the amount of digestion noted in 24 and 48 hours.

TABLE I

Gastric analyses obtained in six patients with diabetes insipidus following a test meal of 50 cc. 8 per cent alcohol with and without Pituitrin injection

Pituitrin						No Pituitrin					
Case	Hours After Test Meal	Volume Juice cc.	Free HCl	Total Acid	Digestion of Egg Albumin		Volume Juice cc.	Free HCl	Total Acid	Digestion of Egg Albumin	
					24 hrs.	48 hrs.				24 hrs.	48 hrs.
1	0	31	42	42	0	0	195	13	15	0	0
	1/2	166	35	42	0	0	19	52	55	0	0
	1	11	20	27	0	0	30	62	68	+++	+++
	1 1/2	13	14	21	0	0	6	45	55	++	++
	2	19	0	7	0	0	17	50	69	++	++
2	0	14	0	6	0	++	23	13	24	0	0
	1/2	52	32	44	0	++	84	28	33	0	++
	1	6	30	45	0	0	21	25	30	0	++
	1 1/2	14	0	10	0	++	25	15	24	0	0
	2	16	0	12	0	+++	11	14	20	0	0
3	0	50	7	17	0	0	33	4	23	0	0
	1/2	38	0	6	0	++	50	24	30	0	0
	1	23	0	8	0	0	8	8	28	0	0
	1 1/2	16	0	8	0	+	7	15	15	0	0
	2	12	0	8	0	+	6	0	10	0	0
4	0	52	20	40	0	0	35	0	6	0	0
	1/2	70	44	56	0	0	40	46	60	0	0
	1	16	31	42	0	++	37	58	60	0	+
	1 1/2	12	28	28	0	+++	23	55	55	0	0
	2	22	7	12	0	0	12	46	46	0	0
5	0	118	20	27	0	0	35	12	24	0	0
	1/2	80	31	34	0	0	62	47	54	++	+++
	1	8	24	32	0	+	37	44	51	0	+
	1 1/2	22	10	16	0	0	16	18	22	0	0
	2	34	4	11	0	0	25	2	12	0	0
6	0	420	17	22	0	0	75	55	67	0	0
	1/2	115	28	30	0	0	108	53	60	0	+
	1	7	10	25	0	0	42	49	66	0	+
	1 1/2	21	17	26	0	0	7	65	75	0	0
	2	21	9	12	0	0	22	24	38	0	0

the chemistry of the gastric juice and in the gastro-intestinal X-rays in eight patients with diabetes insipidus who had marked gastric symptoms. This paper presents the results of these observations.

## METHOD OF INVESTIGATION

This investigation was made by studying the gastric analysis and the proteolytic activity of the gastric juice in six patients with and without pituitrin administration. Gastro-intestinal X-rays were obtained in four cases.

At first, the gastric analyses were determined by obtaining the gastric juice fasting and at half hour intervals for two hours after the ingestion of 50 cc.

When it was found that very little, if any, digestion of egg albumin occurred following the alcohol test meal, the gastric analyses were repeated again in five cases on later days using 0.5 cc. histamine intramuscularly instead of the alcohol meal. In addition, the rennin activity was determined by the clotting of milk. Various dilutions of each specimen of gastric juice were made ranging from 1:40 up to 1:80,000. Then to 5 cc. of diluted gastric juice, 5 cc. of fresh milk and 2 cc. of CaCl<sub>2</sub> were added. These were mixed and incubated at 37° C. for 30 minutes. Coagulation indicated a positive test for rennin. The gastric analyses were made four to six times in each patient. The results were controlled by doing the same gastric analyses with and without pituitrin injection in eight

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normal persons with similar age as the patients with diabetes insipidus.

### RESULTS

The results of the gastric analyses obtained with the alcohol test meal in patients with diabetes insipidus are given in Table I. In the tests without pituitrin therapy, there appeared to be a greater amount of gastric juice and the free HCl than is customarily found in normal people following such a test meal. The administration of pituitrin decreased the acidity of the gastric juice during the test period and also diminished its volume an hour after the injection of the drug. There was no obvious digestion of the egg albumin, with few exceptions, at the end of 24 or 48 hours in most of the specimens of gastric juice whether or not pituitrin was administered. Since I (1) have shown that alcohol inhibited the proteolytic activity of gastric juice, it appeared that the alcohol might account for some of these results although it did not seem likely as late as one and one-half or two hours after the ingestion of this dilute alcohol. The alcohol appeared to stimulate a good amount of acid but not proteolytic enzymes.

It seemed of interest to determine whether another type of gastric stimulus would produce different results. Consequently, histamine was used. These findings are interesting and are given in Table II. In these tests without pituitrin, histamine produced a large volume of gastric juice with a high degree of acidity and marked proteolytic activity in most specimens. These findings were definitely more marked than in the control tests in normal people as shown in Table III. The gastric juice from patients without pituitrin caused a marked or complete digestion of the egg albumin in most instances. In the patients with marked gastric symptoms the rennin test was positive in many of the specimens in a dilution of 1:80,000 of gastric juice. The degree of acidity and of rennin and peptic activity did not always run parallel. In contrast, in the normal controls the rennin

test was usually positive in dilutions of gastric juice ranging from 1:1,000 to only 1:8,000.

The administration of pituitrin shortly before the testing decreased the gastric acidity and either the peptic or rennin effect in the patients with diabetes insipidus and in the normal individuals. In general, there was a greater amount of digestion when pituitrin was not administered.

In comparing the results of the gastric analysis in the patients with diabetes insipidus following the alcohol test meal and the administration of histamine, it is obvious that these two drugs stimulated the volume and acidity of the gastric juice to about the same extent. However, histamine produced gastric juice with a marked proteolytic effect whereas alcohol did not.

The X-rays of the gastro-intestinal tract in four patients with marked gastric symptoms without pituitrin therapy were normal in three cases. The esophagus appeared normal. The stomach was smooth in outline with good peristalsis and no residue in six hours after the ingestion of the barium. The duodenal cap, ileum and cecum were normal. In a fourth patient the X-rays revealed a duodenal ulcer. Although far fetched, this case may be of interest because of the possible relation between certain brain lesions and peptic ulcer.

### COMMENT

The cause of the gastric symptoms in many of the patients with diabetes insipidus is conjectural. However, from the results of these experiments, patients with diabetes insipidus appear to have, following certain stimulation, a greater volume of gastric juice with a higher degree of acidity and an increased pepsin and rennin content than in the normal person. The injection of pituitrin inhibited these effects. Because of these findings, it would seem that the posterior lobe of the pituitary gland has some control over the gastric secretion. As the result, in diabetes

TABLE II

Gastric analyses obtained in five patients with diabetes insipidus following the injection of 0.5 cc. histamine with and without Pituitrin administration

Case	Hours After Histamine	Pituitrin						No Pituitrin					
		Volume Juice cc.	Free HCl	Total Acid	Digestion of Egg Albumin		Rennin	Volume Juice cc.	Free HCl	Total Acid	Digestion of Egg Albumin		Rennin
					24 hrs.	48 hrs.					24 hrs.	48 hrs.	
1	0	83	32	46	0	0	1-80,000	6	0	20	0	0	1-10,000
	1/2	75	73	84	marked	marked	1-80,000	22	68	82	total	total	1-20,000
	1	14	54	62	marked	marked	1-80,000	8	60	80	total	total	1-40,000
	1 1/2	4	30	50	0	0	1-80,000	2	50	75	+	+	
	2	28	11	28	0	+	1-80,000						
2	0	17	6	22	0	+	1-40,000	3	90	100	+	+	1-40,000
	1/2	82	88	99	total	total	1-80,000	65	114	124	total	total	1-80,000
	1	29	91	102	total	total	2-40,000	54	139	142	total	total	1-80,000
	1 1/2	3	100	105	++	total	1-10,000	28	114	122	total	total	1-80,000
	2	22	8	18	0	+	1-80,000	7	100	110	+	total	1-80,000
3*	0	6	0	0	0	0	1-200	13	0	10	0	+	1-200
	1/2	5	25	31	0	0	1-4,000	28	52	64	+	+	1-2,000
	1	5	0	20	0	+	1-8,000	12	30	33	0	+	1-1,800
	1 1/2	18	0	6	0	+	1-400	7	0	8	0	0	1-400
	2	8	0	5	0	0	1-100	6	0	10	0	0	1-40
4	0	110	20	26	0	0	1-20,000	17	0	4	0	0	1-20,000
	1/2	84	62	73	+	+	1-20,000	90	65	70	marked	total	1-80,000
	1	32	46	55	++	+	1-40,000	6	70	80	marked	total	1-80,000
	1 1/2	5	5	15	0	0	1-40,000	5	15	25	0	+	1-80,000
	2	33	0	7	0	0	1-20,000	40	0	14	+	+	1-80,000
5*	0	38	35	48	+	+	1-8,000	30	31	50	+	+	1-8,000
	1/2	22	26	44	marked	total	1-4,000	98	117	126	total	total	1-8,000
	1	62	90	96	marked	total	2-2,000	85	104	111	total	total	1-4,000
	1 1/2	6	60	80	+	+	1-4,000	30	87	89	total	total	1-4,000
	2	12	25	40	0	0	1-4,000	11	45	50	0	0	1-4,000

\*Cases 3 and 6 had no special gastric symptoms.

insipidus where there is a lack of posterior lobe secretion, there is an increase in certain constituents of the gastric juice. This fits in with some observations of Dodds and associates (2) who found in animals that the stimulating effect on gastric secretion by various stimuli is abolished by an extract of the posterior lobe of the pituitary gland. The volume of juice is primarily affected. They also found that the response to histamine in hypophysectomized animals differed markedly from normal and concluded that the rôle of a substance secreted by the posterior lobe of the pituitary is essential for the normal regulations of gastric secretion. In addition, DeAnciaes (3) found that pituitrin decreased the gastric secretion with its acid content in normal persons. Since recent studies in gastro-enterology suggest a correlation between certain cerebral lesions and gastro-intestinal disturbances, it may be suggested that the neurological lesion of diabetes insipidus may cause gastric symptoms. However, no definite conclusions concerning this can be made because there are so few cases of diabetes insipidus.

Water intoxication as a cause of gastric symptoms should be considered here. Nevertheless, I do not believe it is the cause of this disturbance because three of my patients with a fluid intake and output of about eight or nine litres a day have not taken pituitrin for two or three years and they have had no stomach complaints. Furthermore, the blood chlorides have been normal in these cases.

Very little or no peptic activity of the gastric juice occurred after the alcohol test meal in these patients. This was in striking contrast to the marked peptic di-

gestion by the gastric juice obtained in the patients after histamine injection even though the acidity and the volume of gastric juice produced by both gastric stimulants were much the same.

### SUMMARY

Because of the frequency of gastric symptoms in diabetes insipidus, a study was made of the chemistry of the gastric juice in six patients with and without pituitrin injection and of the gastro-intestinal X-rays in four cases.

There was found in diabetes insipidus, changes in the chemistry of the gastric juice which may account for the gastric symptoms. These changes were characterized by a greater volume of gastric juice, a higher degree of acidity and an increased pepsin and rennin content than is ordinarily found in normal people. The administration of pituitrin decreased these findings.

Gastro-intestinal X-ray studies in four patients with marked gastric symptoms showed normal conditions in three cases while in the fourth case there was revealed a duodenal ulcer.

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TABLE III

Control Tests—Gastric analyses obtained in eight normal people following the injection of 0.5 cc. histamine with and without Pituitrin administration

Pituitrin							No Pituitrin						
Case	Hours After Histamine	Volume Juice cc.	Free HCl	Total Acid	Digestion of Egg Albumin		Rennin	Volume Juice cc.	Free HCl	Total Acid	Digestion of Egg Albumin		Rennin
					24 hrs.	48 hrs.					24 hrs.	48 hrs.	
1	0	1	0				1-4,000	9	0	15	0	+	1-2,000
	1/2	7	30	35	0	0	1-8,000	25	60	70	total	total	1-4,000
	1	15	28	30	0	0	1-4,000	4	50	60	+	+	1-2,000
	2	3	0	20	0	0	1-2,000	6	0	20	+	+	1-2,000
2	0	30	39	54	+	+	1-4,000	27	20	34	0	+	1-2,000
	1/2	38	61	67	moderate	marked	1-4,000	99	59	67	moderate	marked	1-2,000
	1	14	45	65	0	0	1-2,000	64	49	58	+	+	1-1,000
	1 1/2	63	24	35	0	0	1-1,000	56	23	31	0	+	1-1,000
3	0	5	0	10	+	+	0	8	0	10	+	+	0
	1/2	17	0	10	+	+	0	5	0	20	+	+	0
	1	4	0	10	0	+	0	9	0	10	+	+	0
	1 1/2	14	0	8	+	+	1-100	14	0	10	+	moderate	0
4*	0	21	18	32	+	+	0	6	0	10	+	marked	0
	1/2	72	73	82	0	total	1-4,000	34	29	53	0	0	1-16,000
	1	42	90	102	marked	total	1-4,000	48	86	102	marked	total	1-8,000
	1 1/2	18	76	90	marked	total	1-2,000	69	91	102	marked	total	1-8,000
5*	0	16	41	54	moderate	marked	1-4,000	13	76	92	marked	total	1-8,000
	1/2	30	7	21	0	0	1-4,000	21	79	90	marked	total	1-16,000
	1	7	10	30	0	0	1-2,000	27	4	16	0	0	1-4,000
	2	13	25	45	0	0	1-4,000	8	65	75	total	total	1-4,000
6	0			26	0	0	1-8,000	5	90	110	+	+	1-8,000
	1/2							10	15	35	0	0	1-8,000
	1							38	0	7	0	+	0
	1 1/2							2	0	10	0	+	0
7	0							12	14	28	0	+	1-32,000
	1/2							40	11	23	0	0	1-2,000
	1							62	0	14	+	+	1-4,000
	1 1/2							26	0	7	0	0	1-500
8	0							51	25	40	+	+	1-20,000
	1/2							7	0	6	0	0	1-20,000
	1							19	0	4	0	0	1-5,000
	1 1/2							23	0	4	0	0	1-5,000
9	0							6	0	20			1-2,000
	1/2							24	0	16			1-2,000
	1							4	0	12			1-500

\*Cases 4 and 5 are healed duodenal ulcers.

# An Abnormal Mechanism for the Excitation of Gastric Secretion in the Dog\*

By

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THE abnormal mechanism for gastric secretion in the dog to be described in this report, we believe, may be concerned in those patients with peptic ulcer which manifest an unusual hypersecretion or a hypercontinuous secretion of gastric juice.

This study was prompted by an observation made by Orndoff, Fauley and Ivy (1) to the effect that three Mann-Williamson dogs which were manifesting a hypersecretion and a hypercontinuous secretion of gastric juice after the development of a jejunal ulcer failed to stop secreting after the subcutaneous injection of 1 mg. of atropine sulphate at hourly intervals for three hours. This was a striking observation because in the dog, atropine in a 1 mg. dose completely annuls the secretory response to a meal for 2 to 4 hours or to all excitatory drugs except histamine and alcohol. This is such a well-established fact in the dog that in order to render tenable the theory that histamine is the gastric hormone, it has been necessary in part to assume that atropine prevents histamine from being formed when secretagogues were acting in the stomach and intestine (3-6). This observation of Orndoff, Fauley and Ivy (1) caused them to suggest the possibility that the hypersecretion might be due to the elaboration of histamine by the irritated jejunal mucosa, in amounts too large to be inactivated by the histaminase in the irritated mucosa. Since the histamine is being elaborated hypothetically as the result of irritation rather than as the result of a normal process such as that occurring after the ingestion of a meal, atropine would not abolish the resulting secretion. Further, irritation of the intestinal mucosa may reduce its natural histaminase content.

## METHODS

Since in the experiments of Orndoff, Fauley and Ivy, gastric analysis was the method used, the failure of atropine to abolish secretion may have been apparent rather than real, due to some retention of juice already secreted. Although this was not likely, we decided to settle the matter by using Pavlov pouch dogs, which to our knowledge is the first time such dogs have been used to ascertain if M-W. dogs manifest a true hypersecretion in response to a meal.

Accordingly, three Pavlov pouch dogs were made. Then, after ten control responses to 100 gm. of ground, parboiled lean beef-hearts were obtained and the effect of 1 mg. of atropine sulphate on the response to the meal was established in each dog, a Mann-Williamson operation was performed. The tests then were re-

peated frequently after the operation until death from ulcer occurred.

## RESULTS

Before operation, in each of these dogs, the secretion of free acid was immediately and completely abolished by atropine; that is, when 1 mg. of the drug was injected subcutaneously while the dog was eating the beef-heart test meal, only a small amount of non-acid secretion was obtained from the pouch over the entire test period. Postoperatively, this characteristic action of atropine was modified by some disturbance in gastro-intestinal function resulting from the operation.

Some of the results obtained on dog 1 are shown in Table I. This dog showed the most marked hypercontinuous secretion of the three dogs. When this dog was manifesting a marked hypercontinuous secretion several days prior to perforation of the ulcer, atropine did not abolish the basal secretion of free acid in a period of two hours, nor did an additional dose of 1 mg. given at the end of this period along with 100 gm. of beef-hearts materially affect the gastric secretory response to the meat meal. Finally, atropine was administered on six occasions in the fourth to sixth hours after ingestion of the test meal, and in no instance was the gastric secretion or the free acidity abolished within an hour. Any interpretation of the results obtained in this dog after operation must be qualified by the fact that there was a definite gastric retention; yet, this fact does not in any way minimize the importance of the fact that the gastric secretory mechanism was very refractory to atropine.

In dog 2, the hypercontinuous secretion was not so marked as in dog 1; yet free acid was secreted for 1.5 hours after the administration of the usual dose of atropine. The secretory response to the meal during this hypersecretory phase could be definitely reduced but not abolished by 1 mg. of atropine.

In dog 3, which did not show a hypercontinuous secretion, the secretion to the test meal postoperatively was not abolished by atropine, as it was before operation.

The failure of dog 3 to manifest a hypercontinuous secretion is not surprising because it has been found that all Mann-Williamson dogs do not manifest the phenomenon or even a hypersecretion to a test-meal; neither do all such dogs manifest a definite increased secretory response to a meal (1). Neither do all patients with "peptic ulcer" manifest a hypersecretion or a hypercontinuous secretion.

Since it was noted that atropine depressed the volume output and to some extent the acidity of the hypersecretion after a meal and the hypercontinuous

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secretion, it is pertinent to present some results on the effect of atropine on the secretion provoked by histamine, histamine being the most likely cause of the hypersecretion observed in the M-W. dog. Accordingly, three Pavlov pouch dogs were given 0.5 mg. of histamine subcutaneously for ten tests and then 0.5 mg. of histamine with 1 mg. of atropine sulphate for a similar number of tests. The results are shown in Table II and are consistent with the results reported in the literature (6), which demonstrate that atropine produces a definite but limited inhibition of secretion or that the inhibition caused by given dose of atropine is less with the greater the histamine stimulus.

Only one of the three dogs, namely, dog 1 (Table I), showed a significant hypersecretion in response to the test-meal.

### DISCUSSION

Pavlov (7) records that one of his students observed a hypersecretion, which occurred after the first hour following the ingestion of a meal, in a dog after the development of a peptic ulcer. He did not test the effect of atropine on the hypersecretion. One of us (A.C.I.) has seen hypersecretion of gastric juice in Pavlov pouch dogs occasionally after an intestinal obstruction, occurring spontaneously, though this is not frequent; also in gastric fistula dogs in which either the pyloric antrum or duodenum is irritated with a

glass or metal catheter. In none of these cases, however, has the effect of atropine been determined.

In the Mann-Williamson dog manifesting a definite hypercontinuous secretion or a hypersecretion or both, in response to a meal, the gastric secretory mechanism reacts to the inhibitory effects of atropine as though a portion of the secretory stimulus is histamine in varying amounts. In man, Pollard (8) has observed that atropine inhibits gastric secretion excited by histamine as in the dog. However, when one reviews the clinical literature (9, 10) on the effect of atropine on the secretory response to a meal in normal and peptic ulcer subjects, a lack of agreement is found, although the majority of observers have found a definite though incomplete inhibition. The apparent inconsistencies may be due to considerations pointed out by Gray (6), or to the possibility that in some normal and peptic ulcer subjects histamine is being produced by some mode of production that atropine cannot counteract.

One cannot conclude from our evidence and the discussion that histamine is the cause of the hypersecretion. Other substances or mechanisms may be produced or exist that may be responsible for the hypersecretion observed or the hypersecretion observed under different conditions (11). It has even not been shown that under irritation the intestinal mucosa produces histamine, though mechanical irri-

TABLE I  
Dog 1 with a Pavlov pouch

Response to Test-Meal Before M-W. Operation. Ave. 10 Tests				Response to Same Meal After M-W. Operation During 12 Days Prior to Perforation. Ave. 7 Tests			
Time	Cc.	Acidity		Time	Cc.	Acidity	
		Mg. Free	Mg. Total			Mg. Free	Mg. Total
0.5 hr.	6.3	15.9	17.5	0.5 hr.	5.4	16.2	19.2
1.0	9.5	29.4	36.3	1.0	9.4	34.4	35.6
1.5	8.6	25.0	32.9	1.5	9.3	36.4	39.8
2.0	6.8	18.6	24.8	2.0	8.8	31.4	38.1
2.5	5.6	13.3	19.4	2.5	8.5	34.0	37.2
3.0	4.3	7.4	12.9	3.0	7.4	29.6	32.4
3.5	3.8	2.7	8.7	3.5	6.8	27.2	29.8
4.0	3.5	1.0	5.7	4.0	5.8	22.2	24.3
Total	48.4	113.3	158.5	Total	61.4	234.4	259.7

Response to Same Meal Before M-W. Operation Plus 1 Mg. Atropine Subcutaneously. Ave. 5 Tests				Response to Atropine Subcutaneously When Animal was Manifesting Hypercontinuous Secretion Prior to Perforation			
Time	Cc.	Acidity		Time	Cc.	Acidity	
		Mg. Free	Mg. Total			Mg. Free	Mg. Total
0.5 hr.	3.1	0	1.5	0.5 hr.	9.1	39.0	40.6
1.0	0.8	0	0.7	1 mg. atropine subcutaneously			
1.5	2.3	0	1.6	0.5	5.3	21.2	22.7
2.0	2.1	0	2.4	0.5	2.7	10.6	11.6
2.5	1.2	0	1.0	1 mg. atropine subcutaneously plus test-meal			
3.0	2.2	0	1.0	0.5	2.5	6.2	8.2
Total	12.0	0	8.2	1.0	6.5	21.3	24.5
The Response to 1 Mg. Histamine Subcutaneously After M.W. Operation				1.5	10.9	43.6	46.7
1 hr.	14.4	44.6	50.0	2.0	5.6	35.3	37.6
				2.5	9.6	41.1	42.9
				3.0	9.5	39.0	40.7
				3.5	9.9	42.3	44.1
				4.0	10.0	30.9	33.7

TABLE II  
Data collected by Dr. Barry

Dog	Ave. 10 Tests with 0.5 Mgr. Histamine			Ave. 10 Tests with 0.5 Mgr. Histamine and 1 Mgr. of Atropine Sulphate		
	Vol. cc.	Free Acidity	Total Acidity	Vol. cc.	Free Acidity	Total Acidity
1	4.0	42	60	2.0	10	25
2	8.0	30	55	3.0	8	20
3	6.1	25	50	3.0	8	27

tation of the pyloric mucosa may excite gastric secretion in a transplanted gastric pouch (11) and though it is believed that the increase in gastric secretion which results after an allergic skin-reaction (12) is due to the production in the skin of an histamine-like substance. The evidence, however, is definitely presumptive, and may explain in part why gastric secretion in some peptic-ulcer patients declines after the ulcer heals or after the administration of bland foods, soothing and mildly astringent substances.

According to existing knowledge, the only other substance than histamine which may be suspected as the cause of a hypersecretion or as a gastric secretory excitant refractory to atropine, is alcohol. It is remotely possible for alcohol to be formed and absorbed if food starch and sugar enter the colon, especially when there is a disturbance of intestinal digestion as in the Mann-Williamson dog. This could be determined by a blood-test for alcohol, which was not done.

#### SUMMARY

The hypothesis is advanced that in some instances of hypersecretory response to a meal or a hypercon-

tinuous secretion of gastric juice, as seen in some ulcer patients and in other abnormal conditions, may be due to an elaboration of histamine by an irritated or inflamed mucosa. This hypothesis is supported by the observation that in three Pavlov-pouch-Mann-Williamson dogs, which manifested a definite hypercontinuous secretion and one of which manifested a definite hypersecretion in response to a meal, the gastric secretory mechanism reacted to atropine as though a portion of the secretory stimulus were histamine.

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## Experimental Studies on the Production of Peptic Ulcers by Vasomotor Alterations (Pitressin Episodes)\*

By

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**P**EPTIC ulcer has occupied the interest of medical men since antiquity. Since the vitality of the mucosa is, under normal conditions, dependent upon three factors, namely: secretion, circulation and innervation, interference with any one or more of these factors experimentally has given rise to erosions, or ulcers; and clinically it is reasonable to suppose that in peptic ulcer these factors are affected.

After sifting through the voluminous literature, the following possibilities suggested themselves. That disturbances in circulation produced in various ways appear to be a prime initial cause in the production of ulcers, and disturbed innervation, the neurogenic factor, among others, plays some part in the subsequent development of chronic ulcers. To study these possibilities, recently discussed by both Petersen (1) as well as Nedzel (2, 3) the following experiments

were carried out. Two groups of animals were subjected to single and repeated doses of pitressin, as in the experiments of Nedzel (3). In one group the animals had been previously vagotomized. The vagi were cut as they passed through the diaphragm and the nerve section observed at necropsy. Dodds (4) has reported ulcerations in rabbits, cats, monkeys, guinea pigs, rats and mice, following injections of an acetone picric acid extract of the posterior lobe. Metz and Lackey (5) have reported fundal lesions of the stomach following injections of pituitrin.

The first phase of our experiments concerns the immediate effect of pitressin in the stomach and duodenum of normal and vagotomized dogs. Pitressin was injected intravenously using 20U per 5 kilogram of body weight with certain variations.

To summarize our results following the intravenous injections of pitressin, a marked spasm of the vessels occurred which was followed by a vascular dilation of

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a rather marked degree then in scattered areas superficial erosions and edema appeared. The experimentally induced disturbance in innervation showed no appreciable effect on the reaction.

The reports in the literature on the effect of pitressin on the motility of the stomach and duodenum are conflicting and are influenced by the method of study. To investigate the influence of pitressin on gastric and duodenal motility, six animals were chosen. After a period of training they were subjected to repeated fluoroscopy, both before and after vagotomy.

The reaction of the dogs of about the same weight to the dose of pitressin as given above, varied somewhat from time to time in the same animal, and varied also from animal to animal. The initial response to the injection of pitressin in all the animals

peristalsis and at other times the forward peristalsis previously described.

In the vagotomized animals the reactions were similar to the controls, with the exception that no reverse peristalsis with vomiting was observed, and the inhibitory period was not quite as long.

In order to determine if the immediate cessation of peristaltic movements following the injection of pitressin might not be due to excitement, injections of equivalent amounts of saline solution failed to produce any observable changes in the peristaltic activities.

With the injection of minute doses of pitressin from 0.01 cc. to 0.15 cc. (0.2 U-3U) only inhibition of peristalsis occurred, lasting four to seven minutes without any subsequent increased peristaltic movements.

In the second phase of the experiment, the results

TABLE I

Dog No.	Number of Injections	Time	Reactions to Injections	Results
1	2	8 days	Very severe	Numerous pinhead to pinpoint size hemorrhagic erosions in pyloric portion of stomach extending up 5 cm. from sphincter.
2	8	30 days	Moderate	No gross changes in stomach or duodenum.
3	8	33 days	Moderate	Two small ulcers in isthmus area near lesser curvature and five small hemorrhagic erosions.
4	8	33 days	Marked	Small ulcer 1 cm. x 0.5 cm. in a hemorrhagic area near lesser curvature 4 cm. from sphincter. Four small erosions in fundus of stomach.
5	9	33 days	Moderate	Five small ulcers in stomach.
6	10	40 days	Moderate	Five definite ulcers in pyloric region and fundus.
7	10	40 days	Severe	Six definite ulcers in pyloric region and fundus.
8	15	50 days	Moderate	No gross changes.
9	8	30 days	Moderate	Six hemorrhagic erosions in stomach.
10	15	78 days	Moderate	No gross changes.
11	10	40 days	Moderate	Four ulcers in pyloric region and three small ones in isthmus region.
12	14	65 days	Moderate	No gross changes.
13	10	35 days	Severe	Numerous pinpoint to pinhead size erosions in pyloric region of stomach and one larger ulcer.
14	25	90 days	Moderate	Small superficial erosion 8 cm. from pyloric sphincter.
15	25	90 days	Moderate	No gross changes in stomach.
16	4	9 days	Severe	Numerous pinpoint to pinhead size hemorrhagic erosions most severe in duodenum and diminishing as it extends down through the jejunum.
17	16	48 days	Moderate	No gross changes.
18	5	16 days	Severe	Severe hemorrhagic duodenitis and jejunitis as described above.

was an immediate cessation of peristaltic movements in the stomach and small intestines. The stomach outline appeared dilated and smooth. In the unoperated animals, the stomach remained atonic for an average of eleven seconds with a maximum variation of from five to thirteen seconds. Following this, movements were first initiated in the duodenum followed immediately by severe and violent peristaltic contractions of the stomach which continued for eight to ten minutes. The contractions were slight at the cardiac end, but increased in severity approaching the pylorus. After this period the stomach had emptied the barium meal and had contracted down. After about five minutes peristaltic movements in the stomach and small intestine returned. In about 15% of the observations, reverse peristalsis with vomiting occurred after the inhibitory period. In some animals a varying response was seen in that at times they would exhibit reverse

of repeated injections of pitressin on the vagotomized dogs were studied and compared with the normal animals. For this study, a group of eighteen vagotomized dogs of approximately the same size and weight were employed. They were compared with a group of normal dogs (presented in a preliminary report by Nedzel) (2) as well as other dogs. Because our preliminary experiments indicated that more than a few injections were required to produce more than a transient erosion, multiple injections were given to produce lesions of greater extent and chronicity.

Two weeks after operation, the animals were injected twice weekly and were given from two to twenty-five injections. (See Table I).

The animals were sacrificed in from thirty to ninety days after the onset of the injections. In twelve of eighteen animals erosions and ulcers were found.



Dog No. 1 showed a marked reaction to his second dose of pitressin and died two days later. Before death it was noted that he had bloody stools. At autopsy, the site of the pathologic changes was in the pyloric region of the stomach extending up about 5 cm. from pyloric sphincter, where numerous pinpoint to pin-head size hemorrhagic erosions, and a moderate edema were found. The remainder of the gastro-intestinal tract was entirely negative.

Eight injections given over a period of a month were found to produce ulcers in five out of six dogs. In five of the dogs the ulcers appeared either in the pyloric region or lower portion of the fundus.

Four dogs were sacrificed after receiving ten injections over a period of forty days. They had from five to seven ulcers, all located in the pyloric and isthmic region of the stomach. The ulcers were larger and deeper than in the previous group.

The last group of dogs were sacrificed, after receiving fourteen to twenty-five injections of pitressin, and from forty to ninety days after the onset of the injections. They were in good health and well nourished and, with the exception of number 14 which showed a superficial gastric erosion, no gross changes were seen in the stomachs.

Two of the animals, No. 16 and No. 18, developed acute bloody diarrhea and died. They were autopsied within an hour after death and presented almost identical pictures. The intestinal canal was filled with blood and beginning sharply at the upper end of the duodenum a marked hemorrhagic duodenitis was found, which extended down with diminishing severity to the ileum. Now, in three of the animals studied, one died of an acute hemorrhagic gastritis, and two of hemorrhagic enteritis with the greatest involvement in the duodenum. In none of the unoperated animals who were given pitressin did this occur.

The microscopic picture varied. In the superficial acute erosion the mucosa showed evidence of acute congestion with dilated vessels filled with blood. At the base and sides of the erosion small hemorrhages were found. The destruction of the tissue extended to the muscularis mucosae. On the other hand, in other erosions the vascular changes were not so marked. The erosions were found in local areas of edema which extended on either side from two to three times the width of the lesion. Near some of these, small lymphocytic accumulations were found.

The deeper ulcers extended down through the submucosa into the muscularis. Microscopically at the base there was present an increase in fibrous tissue with scattered round cells and scattered dilated vessels, at the margins a fibroblastic proliferation and infiltration of plasma cells were seen.

The literature on the histology of the lesions produced by sectioning the nerves to the stomach as well as by injections of adrenalin is conflicting. Dalla Vedova (6) and Durante (7) operating on the splanchnics, produced lesions that were hemorrhagic in character and others in which no hemorrhage could be found with slight reactive phenomena. Some men have reported an inflammatory base with vascular changes, while others have reported slight reactive phenomena.

In the third group of six animals that were vagotomized, but were not given pitressin, no evidence of ulceration was found, after being sacrificed from

thirty to ninety days following operation. This confirms the findings of Ivy (8) and others who failed to find evidence of ulceration in vagotomized dogs.

In comparing the normal animals that were injected under the same conditions as the vagotomized group, we found that ulcerative lesions were produced in 34% of the first group as compared to 67% of the second group. The unoperated animals required more injections, and the ulcers were usually not as deep nor as extensive as in the vagotomized group, although in one animal a large gastric ulcer appeared. Microscopically, the ulcers of the unoperated dogs resembled those that were vagotomized.

In the development of the ulcers, we have in both the operated and normal groups of animals the initial spasm of the vessels produced by pitressin directly and the spasm produced indirectly as a result of muscular contractions, following which dilation occurs. In some cases rupture of a small vessel in the submucosa and a superficial erosion occurs, or localized areas of edema were found following the ischemia. These small necrotic areas are digested by the gastric juices and superficial ulceration may occur. If further spasms do not occur, except as in the particularly reactive animals cited, this lesion heals. With the occurrence of further vascular episodes, the development of an ulcer in certain proportion of the animals follows. The deeper ulcers are similar to those found in humans. With the disturbance in innervation as a result of cutting the vagi, the ulcers developed more rapidly, more frequently, and more extensively. It appears that in the interval between injections the tissues did not recover as rapidly as in the normal dogs. Aschoff (9) pointed out that ulcers did not heal as rapidly in the vagotomized dogs and he felt that the loss of tone of the whole stomach and the decrease in its contractility added considerably to the diminution of the healing tendency. With a disturbance in balance of the vasomotor fibers due to the cutting of the vagi, local spasms (10) leading to impaired vascularity may occur, thus leading to impaired nutrition and diminution of the healing power.

However, with one exception, in one of the dogs reported by Nedzel (3) long standing chronic peptic ulcers have not been produced. Among other possible factors contributing to this may be cited the diminishing reaction to pitressin following repeated injections, and the gradual resumption of function in the vagotomized animals.

The significance of vascular changes (1, 9, 10, 11) in the etiology of peptic ulcer has been brought forth from time to time as well as the increased vaso-motor and nervous instability frequently found in the ulcer patients (10, 12). Suggestive are the observations of the increase in vascular instability occurring in the seasons when peptic ulcer is found to occur or recur with greater frequency (1, 3).

## SUMMARY

Single injections of pitressin produce vasomotor episodes (vascular spasm and relaxation) with scattered superficial erosions or localized areas of edema in the stomach and duodenum. These occur in both normal and vagotomized animals.

Injections of pitressin produced first inhibition of gastric peristalsis which is followed by severe peris-

taltic movements, occasionally reverse peristalsis with vomiting results. Sectioning of the vagus but slightly modifies this response. Minute doses of pitressin produce only inhibition.

With frequent injections of pitressin lesions of the stomach are obtained in normal and vagotomized animals. However, in the vagotomized group, ulcerations are obtained in a greater percentage of cases (67%), and the lesions are more extensive. With one exception, long standing chronic ulcers, were not produced.

Microscopically, some of the ulcers extend down into the muscularis.

In a group of animals that were vagotomized but were not injected with pitressin no ulcers were obtained.

Our experimental results suggest the possibility although not conclusive that vascular alterations of a functional nature particularly in an individual with a constitutional habitus characterized by increased irritability and vasomotor instability, may play a role in the etiology of peptic ulcers.

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## Clinical Notes on the Use of Immunized Donors in Chronic Bacillary Dysentery\*

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IN previous communications (1-4) attention was called to the use of individuals who have recovered from bacillary dysentery as donors for patients with the acute or chronic form of the disease. At that time we attempted to keep on file at the hospital all Blood Betterment Association donors whose serum exhibited titers against *B. dysenteriae*. Owing to the relatively sparse supply of suitable donors and the inability of the Association to keep them segregated and readily available for the purpose indicated, another method was devised. This consisted in actively immunizing compatible volunteers with D-C vaccine (*B. dysenteriae*, hemolytic and non-hemolytic *B. coli*, enterococcus) using, wherever possible, strains recovered from the patient by crypt aspiration culture (5). In other instances, recently isolated cultures of *B. dysenteriae* indigenous to the area were used. In either case, the organisms were fortified by polyvalent strains isolated from patients with acute bacillary dysentery or chronic ulcerative colitis. Where cultures for *B. dysenteriae* proved negative, we chose those dysentery strains against which the patient's serum exhibited the highest agglutination titer.

The vaccine is prepared in a concentration of one billion per cubic centimeter and the organisms subjected to the minimal lethal temperature for a sufficient period to insure sterility. This method provides

a vaccine of relatively high antigenic potency. A healthy donor belonging to the same blood group is tested for sensitivity by means of a one minim intradermal test, following which he is inoculated at three day intervals with 0.3, 0.5, 0.7, 0.7 and 1 cc. respectively. Three to five days after the last injection a 500 cc. transfusion of the donor's unmodified blood is given the patient by the direct method.

We have found the blood of immunized donors particularly useful in very sick patients who cannot respond to active immunization themselves. Serological and cultural studies indicate that a definite rise in agglutinins and bactericidal power occurs in both donor and recipient, but that they do not persist for as long a period in the patient as when direct active immunization is carried out. In order to supplement this method of therapy we are preparing large rabbits in a similar manner. They will be bled only when needed in an emergency where the time element is an important factor. By keeping the blood titer high and collecting the serum only as required we hope to attain the same general favorable response with rabbit serum as with unmodified human blood.

The general question of immunized donors has been the subject of considerable critical comment. In such diseases as subacute bacterial endocarditis they have proved valueless, largely by reason of the underlying pathology. In chronic ulcerative colitis the ideal method of approach to the infected intramural

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Submitted August 17, 1939.

structures is by the hematogenous route. A critical comparison of the use of immunized donors blood with non-immunized donor controls during the past five

years indicates, in our experience, the greater value of the former as a supportive measure in chronic ulcerative colitis.

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## Editorial

### A PECULIAR REACTION OF BLOOD VESSELS IN PATIENTS WITH HYPERTENSION

FOR years research workers have hunted for something peculiar about the reactions of blood vessels of patients with hypertension. Today it is pretty well recognized that in most cases hypertension is the result of an increased peripheral vascular tone. This is doubtless based on some hereditary peculiarity, but just what causes the increased vascular tone is still unknown. The return of hypertension after section of the splanchnic nerves shows that the vasoconstrictors are not basically at fault. Search for some humoral pressor substance in the blood of patients with hypertension is in progress, but as yet the evidence is against this theory.

In a recent paper in the November, 1939, number of the American Journal of the Medical Sciences, Engle and Binger report the interesting observation that the peripheral blood vessels of most hypertensive patients react by a greater dilatation in response to the administration of acetyl-beta-methylcholine than do the blood vessels of normal individuals. It is difficult to understand how peripheral blood vessels which display a hyperdilatation in response to the administration of

choline derivatives can be maintained in a state of increased tone in the case of hypertensive individuals, unless one assumes that the concentration of acetylcholine at the nerve-endings of the cholinergic vasodilator nerves of these patients is subnormal. Engle and Binger present their observations in support of the hypothesis that a deficient acetylcholine-vasodilator mechanism may be a factor in the production of the arterial hypertension of man. This approach to the study of mechanisms for the production of hypertension looks hopeful and further investigation should be done along this line.

In the January, 1940, number of the Journal of Clinical Investigation, Drs. Eugene Stead and Paul Kunkel reported experiments which indicate that in arterial hypertension the peripheral resistance is uniformly raised throughout the area of the greater circulation, but it is not increased in the splanchnic area to any greater extent than in other parts of the body. These authors studied the blood flow in the hand and foot at 43° C. and in the muscles of the forearm after exercise and could see no difference in the reactions of normal and hypertensive persons.

W. C. A.

## Book Reviews

*An Introduction to Gastro-Enterology (The Mechanics of the Digestive Tract)* 3rd ed. By Walter C. Alvarez. New York, Paul B. Hoeber, Inc., Medical Book Department of Harper and Brothers, 778 pp. Price \$10.00.

HERE is an unusual book, written with sufficient technical detail to interest every physiologist working on problems of the mechanics of digestion, and yet written in such simple English and with such knowledge of the needs of the practicing gastro-enterologist as to greatly interest him. Such a book could have been written only by a man like Alvarez who has been at the same time a consulting internist with a wide experience and a research physiologist who has contributed much to our knowledge of the movements of the stomach and intestine.

The second edition of "The mechanics of the digestive tract," published in 1928, was soon sold out. Now the book reappears completely rewritten and brought up to date. It is now a large volume of nearly 800 pages. There are seven new chapters and there is a remarkable bibliography of some 2300 titles. The

articles and books quoted appear all to have been used in the writing of the book. The book is attractively printed and has 186 illustrations. It should be a source book to quarry from during the next fifty years.

The bibliography alone is of such value that every physiologist will want to have a copy of the book on his desk. If he wants to find Bayliss and Starling's classic articles, or Cannon's paper on the acid control of the pylorus or Boyden's first paper on the effects of egg yolk and cream on the gall bladder, he can get the reference in a moment.

Of great value to all young readers and perhaps to their elders will be the chapter on where to look in the library for valuable articles, and especially reviews of the world's knowledge on different topics. One finds in the book remarkably complete abstracts and summaries of the world's knowledge in regard to the movements of the stomach, the control of the pylorus, the movements of the small and large intestine, the control of the ileocecal sphincter, the mechanisms of defecation and vomiting, the mode of

production of flatulence, and the innervation of the digestive tract. Particularly interesting to gastro-enterologists will be the summaries of the world's knowledge in regard to the mode of production of the several symptoms of indigestion.

One can find out how and why food goes down the digestive tract; why gas forms or where it comes from; why sometimes there is marked spasm at the cardia or in the sigmoid colon; why and how ulcers and gall stones produce pain, and why some persons are constipated. Some readers may object that here and there no positive opinion is given on a question, but Alvarez likes to give both sides of an argument, and when sufficient information was not available for the drawing of a conclusion, he bluntly says so.

Alvarez admits that in the past his thinking was not entirely clear on the gradient question in that he confused the gradients and the "polarity" of the bowel and talked of them as if they were synonymous. Now he states that there can be no question about the gradients; they are there and many men have seen them. Furthermore, the intestine is unquestionably "polarized" so that every part conducts better in one direction than another. The gradients probably have something to do with the polarization, but just what the connection is, no one yet knows.

In regard to the old controversy as to the mechanisms directing the rhythmic movements of the small bowel, Alvarez again tries to be fair to the protagonists on both sides. Although he shows that practically all the evidence now indicates that smooth muscle could contract rhythmically by itself if it had to, he admits that as yet no one has been able to get rid of an intramuscular network of fine nervous fibrils. Under these circumstances the advocates of a nervous pacemaker have a right to their opinion. Some evidence indicates that during life the nerves step up the pace of the rhythmic contractions; when they have been benumbed by anoxemia or nicotine, the muscle beats at a slower rate, probably by itself. The dispute is of little consequence because in the normal bowel the nerves are present and they are serving useful functions.

For the convenience of hurried readers each chapter carries a summary at the end. Certainly any man who wants to educate himself in the fundamentals of gastro-enterology can save himself years of library research by reading this book.

*Diseases of the Gall Bladder and Bile Ducts.* By Waltman Walters and Albert Snell. Philadelphia, W. B. Saunders Company, 645 pp., 342 illus., 1940. Price \$10.00.

HERE is a delightful book and one that every gastro-enterologist in the world will want to own. In the first place, it is written by men who have had an enormous experience in this field and who know whereof they speak. Drs. Walters and Snell, one a surgeon and the other a clinician, have gathered within the covers of this book everything of value that has been learned about gall bladder disease at the Mayo Clinic in the last forty years. One of the great values of the book is that it represents actual experience at the bedside and not quotations from the literature. In fact, our only criticism of the section on medical treatment of cholecystitis is that Dr. Snell

has been too kindly, too unwilling to say that he thinks some widely used treatments are of little value and that he wouldn't think of using them himself.

There are several fine chapters by Higgins and Bollman on the anatomy and physiology of the gall bladder, by MacCarty on pathology, by Kirklin on cholecystography, by Butt on pre- and postoperative care in the management of complications, by Magath on the determination of prothrombin clotting time, by Gray on postcholecystectomy syndromes and by Sister William on the technic of the operating room.

One of the fine features of this book is that in planning the chapters the authors have broken away from old classifications and have dealt with facts as they have found them in the Clinic. For instance, in the older books one would probably search in vain for information in regard to the commonly seen post-cholecystectomy syndromes or on the highly important subjects of the preparation of the jaundiced patient for operation and his care by the surgeon and the clinician after operation.

Many of those men who have found it hard to believe that serious operations on the gall bladder can be done at the Mayo Clinic with the mortality around 2 per cent do not realize how much of this low mortality is due to the close cooperation between clinicians and surgeons, both before and after the operation. They do not know that lung specialists, highly trained in the handling of beginning pneumonias, are watching the lungs, and men highly conversant with the problems of blood clotting are watching the prothrombin time. Others with a wide experience in handling patients who retain some symptoms after cholecystectomy are also standing by ready to help.

As one would expect from Snell's training and experience, the chapter on medical treatment is conservative. As Snell says, most of the patients who come to the Mayo Clinic knowing that they have gall bladder disease are seriously ill, and one can't hope to accomplish much for them by any medical treatment. Snell admits that it is conceivable that one can do something medically for the patient who is not very ill, but when he gets better one can't tell whether the pills or nature worked the cure. As Snell says wisely, when a man or woman has gall stones, the logic of giving a cholesterol-low diet is not clear because it is like locking the stable after the horse is stolen. Some physicians might answer that a physician should try to protect the patient from further gall stone formation, but actually the pathologist tells us that in most cases the stones in the gall bladder are so much alike that they probably were all formed at one time and on one occasion. Only rarely is there any sign that the calculous gall bladder tends to produce more stones.

The chapter on the possible formation of gall stones is excellent. The conclusion is that if only because there are several types of stones, it is impossible to explain their formation with one hypothesis.

Dr. Snell hasn't much enthusiasm for duodenal drainage either from the diagnostic or the therapeutic points of view.

Kirklin brings out the important point that one shouldn't pay much attention to small changes in the filling or emptying of the gall bladder. As he says, "In all cases, judgment as to a normal response should be

liberal, for there is no standard normal as to size or density of the shadow, and its best appearance as well as its worst should always be given consideration." "Accelerated or retarded filling or emptying of the gall bladder is not a safe basis for the diagnosis of disease."

One of the most valuable chapters and one that every gastro-enterologist will want to read is Chapter 9 on the differential diagnosis of conditions associated with jaundice. This alone together with the little diagrams on pages 354 to 359 is worth the price of the book. Valuable also is the discussion of the selection of cases for

operation. Right up to date is the chapter by Walters and Butt on the use of cholangiography. Excellent also is Walter's discussion of strictures of the common duct. He has operated on over 100 patients with this very serious disease.

The book is beautifully printed, beautifully illustrated and well documented. It has an excellent index.

*A Synopsis of the Diagnosis of the Acute Surgical Diseases of the Abdomen.* By John Hardy, St. Louis, C. V. Mosby Company, 345 pp., 1938.

Here is an attractive, handy, flexibly bound little book of 345 pages

which a physician might do well to slip into his emergency bag because it can help him greatly in thinking over the various diseases which might be present to account for an acute abdomen or an acute attack of abdominal pain. The book is attractively printed and has many useful illustrations. There is a tremendous amount of information between its covers. It can be recommended highly.

*How Ancient Healing Governs Modern Therapeutics.* By Kleanthes A. Ligeros, New York, G. P. Putnam's Sons, 523 pp., 1937. Price \$10.00.

This is a delightful book which should interest every physician with a flair for the history of medicine. Dr. Ligeros is obviously well acquainted with the literature of the ancient Greeks. In several chapters he discusses every bit of medical knowledge which is revealed in the Iliad, the Odyssey, and many of the writings of the great philosophers, poets and playwrights of Greece. It is interesting to see how much of medicine was known in those old days, hundreds of years before the birth of Christ, and it is startling to see how much the medical theories of these old Greeks influence our thought and speech and medical practice today. When a modern physician gives a needless and often harmful purge to a child coming down with measles or influenza he does not know it, but he is thoughtlessly following in the footsteps of some ancient Greek who always began every treatment with the purging out of a "peccant humor." The book is well printed and well illustrated.

*The Effect of the Macallum-Laughton Duodenal Extract Upon Hypophyseal Diabetes.* By Joseph Marshall Flint and Louis Michaud, London, Ontario, Canada. Published by A. B. Macallum, 77 pp.

This is a mimeographed book in which the authors report a detailed metabolic study of a patient with an insulin resistant hypophyseal type of diabetes. The patient was treated with the Macallum-Laughton duodenal extract. Evidently this extract, when potent, is effective in some of these hypophyseal cases. It seems to overcome resistance to insulin and it is synergistic with insulin. It has a prolonged action, and curiously, this action may be considerably delayed in its appearance. It stabilizes the blood sugar level and it improves the utilization of sugar by helping remove it from the blood. It has a short and a long action, and it tends to prevent the rebound after the transitory action of insulin. This little monograph will be of interest to all of those who treat diabetes.



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**T**HE VALUE of irradiated evaporated milk as a prophylactic source of vitamin D is indicated by the comprehensive study quoted above. Physicians are invited to write for reprints of this article; also for book,

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# The Effect of Various Antacids on the Hydrogen-Ion Concentration of the Gastric Contents\*

By

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and

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## INTRODUCTION

THERE is an increasing amount of evidence to indicate that acid gastric juice plays a significant role in the pathogenesis and non-healing of gastro-duodenal ulcer (1-3). The important problem of ulcer therapy, therefore, seems to be that of controlling the reaction of the gastric contents. Alkalies have been used extensively for this purpose (4) but there is very little evidence as to the degree of neutralization actually obtained. The purpose of this study was to appraise the *in vivo* neutralizing effect of a group of commonly used antacids.

Some early writers (5-7) have contended that antacids stimulate gastric secretion whereas others (8-11) have reported an inhibitory effect. More recently, Crohn (12), Lockwood and Chamberlin (13) and Boyd (14) have supported the contention that alkalies increased gastric acidity, while Keefer and Bloomfield (15) found that alkalies quantitatively neutralized the gastric contents. The first scientific attempt to control continuously the reaction of the gastric contents was made by Sippy (16) in 1915, with the administration of milk and cream and alkalies at hourly intervals. Although this program has been shown to neutralize completely the free acidity in many instances (17), Palmer (18) found many cases in which it was difficult, if not impossible, to obtain satisfactory neutralization. Wosika (19) obtained similar results. Foldes (20) has inferred that the Sippy program stimulates gastric secretion.

## METHOD OF STUDY

During the past two years a total of 290 experiments, each of 10 hours duration, have been conducted on 25 adult male patients with healing duodenal ulcers. A Rehfuß tube was maintained constantly in the stomach for each experimental period. Preliminary observations were made with the patients on a three meal general diet and on a schedule of hourly feedings of 3 ounces of an equal mixture of milk and cream. The method of study was as follows:

1. Ten to fifteen cc. quantities of gastric contents were aspirated every hour from 7 a.m. to 5 p.m.; control samples were removed daily at 7 and 8 a.m. before the administration of the various antacids.

2. Three ounces of an equal mixture of milk and cream were taken hourly after each aspiration from 8 a.m. to 4 p.m. This schedule was kept constant throughout the entire study.

3. Alkalies were given in the amounts indicated on

the charts every hour on the half hour from 8:30 a.m. to 4:30 p.m.

4. The effect of atropine on gastric acidity was studied alone and in combination with various antacids. The atropine was administered by mouth in 1 milligram amounts at 8:30 a.m., 10:30 a.m., 1:30 p.m. and 3:30 p.m.

5. The patients were maintained at moderate hospital activity. They were instructed to avoid swallowing saliva and also to keep records of their use of water and tobacco. No alkalies were taken beyond the experimental period.

The occasional presence of bile in the aspirations did not affect the general results.

The hydrogen-ion concentration of each sample of gastric contents, in the first 120 experiments, was measured with a McInnis glass electrode and a type K potentiometer, the electromotive force being amplified by the F.P. 54 Pilotron tube. Measurements were made at 25° Centigrade plus or minus 1° C. A standard acetate solution, Ph 4.62, was used as reference. This method gives values accurate to 0.01 of a pH. In the last 170 experiments, determinations of the hydrogen-ion concentration were made with the Beckman pH meter which has a claimed accuracy of 0.05 of a pH. This method of measuring gastric acidity is not only more rapid but also more accurate than the usual titration procedure.

The question as to what constitutes "adequate neutralization" is difficult to answer. According to Michaelis (21), most of the free HCl is neutralized at pH 3.0. Helmer (22) and Martin (23) consider a pH of 4.0 to represent adequate neutralization. Hollander (24) writes: "If we desire to eliminate only the free acidity from a patient's stomach by administering some kind of antacid, any pH above 3.0 or 3.5 will be effective for the purpose, whereas for the elimination of total acidity, the pH must be elevated to 7.0. In a study of antacid neutralization, on the other hand, we ought to focus our attention on acidity in relation to pepsin activity and define the effective neutralization point ("proteolytic neutralization point") as that pH at which the pepsin is practically inactive, or a value of at least 5.0." In this particular study, we have arbitrarily considered a pH of between 4.0 and 5.0 as indicative of effective control of the gastric acidity. It is entirely possible, however, that the healing of a gastro-duodenal ulcer may occur at a lower pH.

Standard deviations (plus-minus) were calculated for each hourly set of figures, and curves were plotted indicating one standard deviation above and one standard deviation below the mean. The area between these lines would include statistically, 67 per cent of

\*This study was supported in part by a grant from the John Wyeth & Brother Company, Philadelphia, Pa.  
†Department of Medicine, University of Chicago.  
Submitted September 26, 1939.

all determinations, no matter how many were made. In evaluating the various antacids, for the sake of clarity, only the average hourly results are considered in the text; the maximal and minimal variations can be noted on each chart.

### General Diet (Chart 1)

Seventeen experiments were completed with a general diet. The food was always served after the 8 a.m. and 12 noon aspirations. The average pH values were: 1.78, 1.56 (controls) 2.45, 2.19, 1.61, 1.66, 2.45, 2.10, 1.42, 1.50, 1.50. It will be noted that a rise in pH occurred after each meal and persisted for two

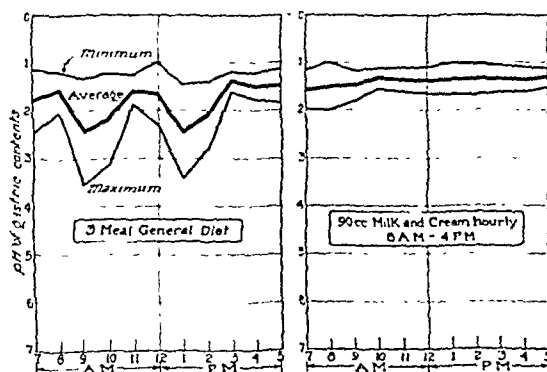


Chart 1. The effect of a general diet (17 experiments) and of milk and cream (20 experiments) on the pH of the gastric contents.

hours. These findings are in agreement with the well-known fact that food can reduce gastric acidity (25). This may result from absorption of the HCl, actual neutralization if the food is alkaline, and by dilution. It is interesting to note that the values obtained in these studies agree closely with the results of test meal filtrates reported by Norgaard (26) as ranging between 1 and 2.

### Milk and Cream (Chart 2)

Twenty experiments with a schedule of hourly feedings of three ounces of milk and cream yielded the

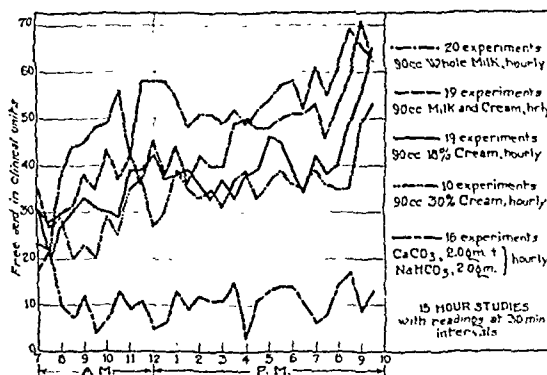


Chart 2. Comparison of effects of milk and cream preparations with varying fat content and an alkaline mixture on the free HCl of the gastric contents.

Footnote: A detailed statistical analysis was not considered necessary for the practical purposes of this study. Calculation of the statistical significance of the effects of the various antacids can easily be made from the data supplied on each graph.

following mean pH values: 1.60, 1.51 (controls) 1.34, 1.37, 1.38, 1.36, 1.36, 1.35, 1.37, 1.33. The pH values were surprising in view of the known neutralizing capacity of milk as shown by in vitro experiments (27). It must mean, we believe, enormous amount of acid is secreted. It seemed while, in this connection, to collect the data numerous half-hourly aspiration studies performed the past few years, using milk and cream prep of varying amounts and concentrations of fat protein. The free HCl in these cases was determined by titration with 0.1 N NaOH. Chart 2 summarizes the average results with milk and cream prep of varying fat content. It will be noted that, with augmented quantity of fat improved the neutralization of free HCl, this reduction was not pronounced compared with the effect of an alkaline mixture: calcium carbonate 2.0 gm. and sodium bicarbonate 2.0 gm. administered at hourly intervals. Chart 3

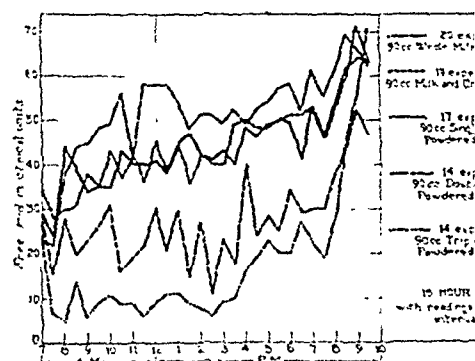


Chart 3. The effect of milk mixtures of varying protein and fat content on the free HCl of the gastric contents.

summarizes the results of 84 experiments, each of 15 hours duration, in which the protein, as well as the fat content of the milk mixtures was varied. The results indicated that the addition of whole milk and cream in the diet indicated resulted in a surprisingly acid reaction of the gastric contents. "Single strength" powder likewise resulted in a high free acidity; when the protein and fat content were increased with "double" and "triple strength" powders there was a definite lowering of gastric acidity. It seems likely in comparing these charts that increased protein content, presumably by increased buffer capacity, accounts for the improved neutralization. Both graphs demonstrate the evening free acidity which will be discussed later. Several studies were made with milk preparations of increasing protein content (Chart 11). The average pH values were: 90 cc. milk with 5 per cent Casein 1.74 (controls) 1.47, 1.44, 1.27, 1.12, 1.57, 1.81, 1.35. 90 cc. milk with 7 per cent Casein 1.74, 1.33 (controls) 1.91, 1.69, 1.53, 1.42, 1.36, 1.30, 1.33, 1.33.

\*The various powdered milk preparations were obtained by Simlac in varying proportions. In these studies:

80 cc. of milk contain...	4.6	1
90 cc. of milk and cream contain...	4.5	2
90 cc. Single strength	3.1	3
90 cc. Double strength	1.1	4
90 cc. Triple strength	0.5	5
90 cc. milk with 5% casein contain...	5	6
90 cc. milk with 7% casein contain...	5	7

In contrast to the previous titration results, increasing the protein content did not elevate the gastric juice pH. We have no explanation for this difference. It is of interest to note that Alley (28) has observed a continuous secretion in two pouch dogs fed with milk or cream repeatedly; cream evoked the more prolonged secretion.

Recently Wosika and Emery reported that 12.5 gm. of a preparation of powdered milk mixed with the usual Sippy powder (calcium carbonate 0.6 gm.) (sodium bicarbonate 2.0 gm.) and given at hourly intervals, was somewhat more effective in neutralizing gastric acidity than 90 cc. of milk and cream and the same powder given in the usual way advised by Sippy. Wosika (30) noted further that alkalized powdered skimmed milk tablets more completely neutralized the free acidity than the routine Sippy procedure. Three experiments with this (Chart 11) preparation,\* one tablet hourly, resulted in the following average values: 2.37 (control) 2.31, 2.12, 1.70, 2.69, 2.88, 2.21, 2.05, 2.59, 1.94. One experiment with three tablets hourly indicates that this preparation possesses definite neutralizing power. The figures: 2.01, 2.22 (controls) 3.87, 2.47, 3.16, 4.24, 4.54, 2.28, 4.00, 4.92.

"Simple Powders" (calcium carbonate 0.6 gm.) (sodium bicarbonate 2.0 gm.) (Chart 4).

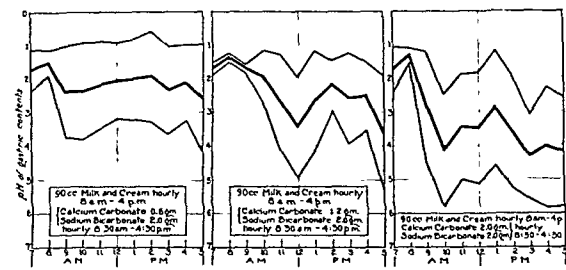


Chart 4. The effect of mixtures of calcium carbonate and sodium bicarbonate on the pH of the gastric contents. (a) calcium carbonate 0.6, sodium bicarbonate 2.0, 20 experiments; (b) calcium carbonate 1.2, sodium bicarbonate 2.0, 6 experiments; (c) calcium carbonate 2.0, sodium bicarbonate 2.0, 16 experiments.

Twenty experiments with this antacid administered hourly yielded the following average pH values: 1.73, 1.51 (controls) 2.38, 2.36, 2.18, 2.06, 2.01, 1.92, 2.34, 2.11, 2.57. The results indicate a slight reduction of gastric acidity when compared with the effect of milk and cream alone.

"Intermediate Powders" (calcium carbonate 1.2 gm.) (sodium bicarbonate 2.0 gm.) (Chart 4).

Six experiments resulted in the following hourly figures: 1.72, 1.36 (controls) 1.69, 1.93, 2.69, 3.45, 2.70, 2.20, 2.58, 2.52, 3.58 signifying improved neutralization of the free acidity.

"Heavy Powders" (calcium carbonate 2.0 gm.) (sodium bicarbonate 2.0 gm.) (Chart 4).

Sixteen experiments revealed that this antacid combination was definitely superior to the preceding alkalies in depressing gastric acidity. The values were: 1.76, 1.32 (controls) 2.85, 4.15, 3.45, 3.48, 2.89,

\*Each tablet contains skimmed milk powder 2.98 gm.  
calcium carbonate 0.74 gm.  
sodium bicarbonate 0.08 gm.

3.59, 4.34, 4.05, 4.18. It is obvious from Chart 4 that the improved neutralization was due to the increased amount of calcium since this was the only factor varied in these three types of experiments. More effective control of the gastric acidity with larger amounts of calcium carbonate, therefore, was to be expected.

Calcium Carbonate 4.0 gm. (Chart 5)

Calcium carbonate in 4.0 gm. quantities was administered at hourly intervals in 26 experiments. The composite hourly pH values show a pronounced neutralization of the free HCl, surpassing all previous

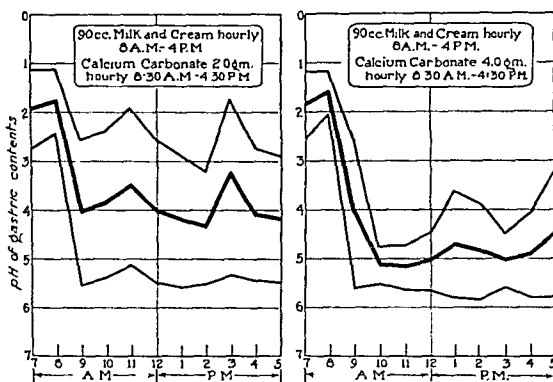


Chart 5. The effect of calcium carbonate 2.0 gm. (15 experiments) and calcium carbonate 4.0 gm. (26 experiments) on the pH of the gastric contents.

antacids both in effectiveness and constancy of action. The values: 1.86, 1.61 (controls) 4.08, 5.14, 5.19, 5.06, 4.71, 4.85, 5.04, 4.93, 4.50 approach most closely the "proteolytic neutralization point" of Hollander. It seemed desirable, therefore, to determine the neutralizing capacity of 2.0 gms. of calcium carbonate omitting the sodium bicarbonate included in the usual Sippy powder.

Calcium Carbonate 2.0 gm. (Chart 5)

Fifteen experiments showed effective control of the gastric acidity. The average hourly results were: 1.91, 1.76 (controls) 4.05, 3.88, 3.53, 4.03, 4.22, 4.37, 3.29, 4.10, 4.19. The question as to whether sodium bicarbonate stimulates gastric secretion cannot be answered definitely by these studies. Boyd (31) found that, in dogs, small amounts of this alkali increased gastric acidity. Lockwood and Chamberlin (13) observed frequently, in man, that sodium bicarbonate in 4.0 gm. doses, in addition to its immediate neutralizing effect, causes a rebound of acidity to a point higher than would occur normally. Seckbach (32) made similar observations, although he concluded that small amounts neutralized the free HCl. In this connection, three experiments with 2.0 gms. of sodium bicarbonate given hourly resulted in a pH range of 1.35 to 3.02, while in two experiments with 4.0 gm. quantities, the values ranged from 1.49 to 4.19.

The few reported studies of the antacid capacity of calcium carbonate are not in agreement. Several investigators (31, 33, 34) noted that, in dogs, in amounts up to 2.5 gm. per kilo body weight, calcium carbonate increased the flow of gastric juice. This effect was



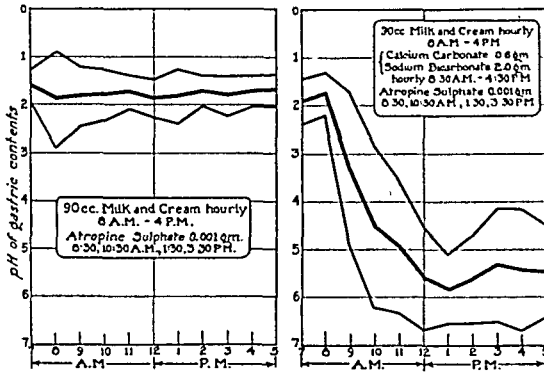


Chart 6. The effect of atropine sulphate alone (17 experiments) and in combination with "simple powders" (15 experiments) on the pH of the gastric contents.

attributed to possible stimulation by carbon dioxide and calcium chloride formed in the reaction with HCl. However, Loevenhart and Crandall (35) and Lockwood (13) were favorably impressed with the neutralizing power of calcium carbonate. Wosika (36) concluded also that "the high calcium tablets seem superior from the standpoint of effectiveness on the gastric acidity."

#### Atropine Sulphate (Chart 6)

Atropine sulphate was given by mouth four times daily in 1 milligram doses at 8:30 a.m.—10:30 a.m.—1:30 p.m. and 3:30 p.m. in seventeen experiments. The hourly pH values averaged: 1.61, 1.89 (controls) 1.83, 1.80, 1.74, 1.86, 1.82, 1.71, 1.80, 1.71, 1.67 indicating no appreciable reduction in gastric acidity as compared with the control observations. Several experiments with a similar amount of atropine administered hypodermically gave identical results. The patients experienced moderate thirst and occasionally had difficulty in aspirating the gastric contents. Although the volume of gastric contents was not routinely measured, it seemed definitely diminished. Quantitative studies of the effect of 1 mgm. of atropine on the gastric secretion evoked by 0.6 mgm. of histamine disclosed no effect on the level of acidity; the volume of secretion, however, was reduced by 35 to 40 per cent. This

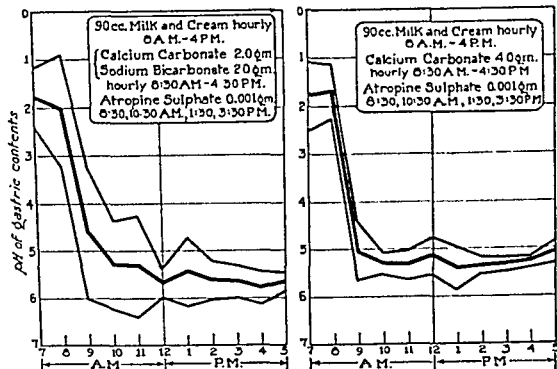


Chart 7. The effect of atropine sulphate and heavy powders (11 experiments) and of atropine sulphate and calcium carbonate 4.0 gm. (7 experiments) on the pH of the gastric contents.

subject is considered in more detail later. It was decided, next, to determine whether the reduced volume of secretion would allow more effective neutralization.

#### Atropine and "Simple Powders" (Chart 6)

Atropine and the powder were used in the quantities previously indicated. Fifteen experiments yielded the following average hourly values: 1.91, 1.75 (controls) 3.32, 4.52, 4.94, 5.59, 5.82, 5.62, 5.32, 5.42, 5.45, representing the most marked reduction in acidity attained thus far. Moreover, this neutralization was almost constantly maintained for the entire experimental period.

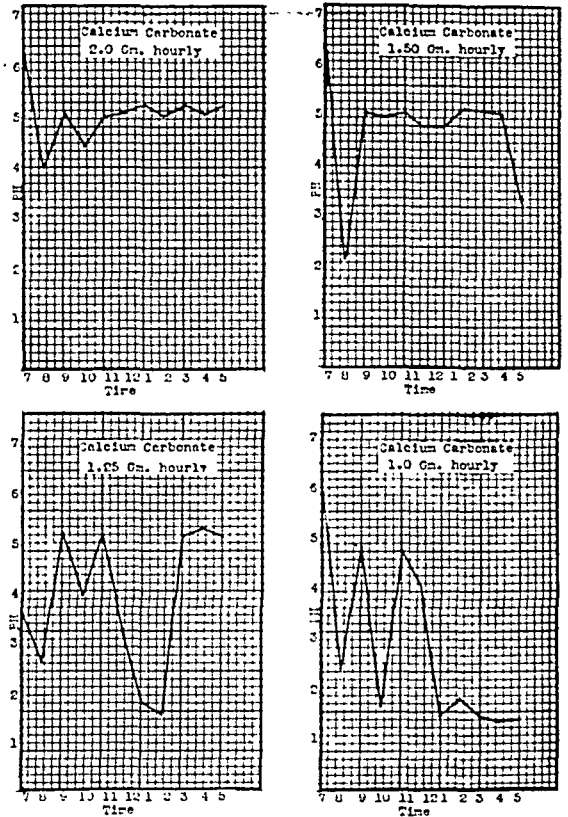


Chart 8. The influence of varying amounts of calcium carbonate on the pH of the gastric contents in one patient.

#### Atropine and "Heavy Powders" (Chart 7)

Eleven experiments with this combination showed even greater depression of the free HCl, the hourly composite values being: 1.80, 2.05 (controls) 4.58, 5.28, 5.32, 5.67, 5.44, 5.63, 5.65, 5.79, 5.66.

#### Atropine and Calcium Carbonate 4.0 gm. (Chart 7)

The results in seven experiments are comparable to those in the two preceding groups. The hourly values were: 1.79, 1.70 (controls) 5.06, 5.32, 5.34, 5.16, 5.42, 5.36, 5.33, 5.28, 5.09. The remarkably constant findings obviated the necessity for further experiments with this antacid combination.

A series of experiments was conducted on one patient to determine the minimum effective amount of

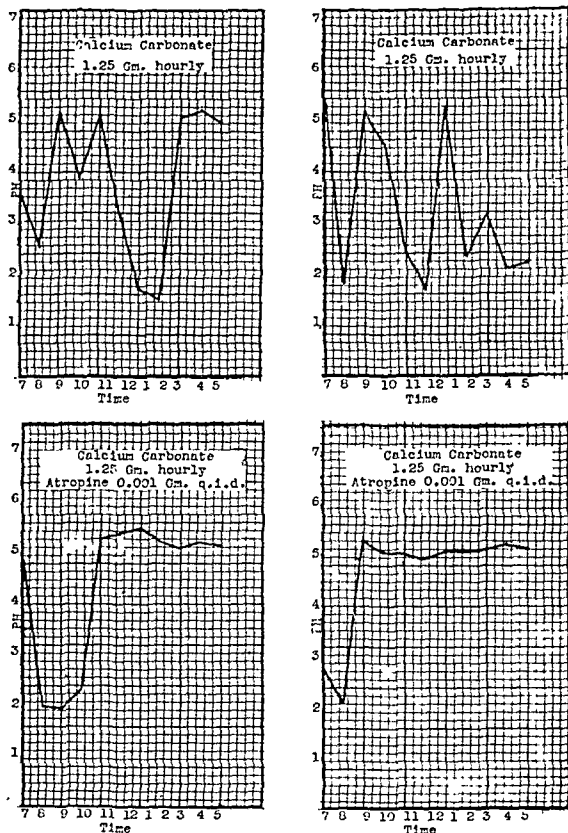


Chart 9. The effect of calcium carbonate 1.25 gm. alone and in conjunction with atropine sulphate on the pH of the gastric contents in the same patient.

alkali required with four 1 mg. doses of atropine to adequately neutralize gastric acidity. The schedule followed was the same as in preceding studies. It will be observed that 2.0 gm. and 1.5 gm. of calcium carbonate neutralized the acidity effectively in this particular patient without the use of atropine (Chart 8). 1.25 gm. calcium carbonate produced partial neutralization while 1.0 gm. was least effective. Two experiments with the patient receiving 1.25 gm. calcium carbonate

hourly and four 1 mg. doses of atropine by mouth (Chart 9) indicated much more effective neutralization as compared with a similar amount of calcium carbonate given alone. This brief study suggests that smaller quantities of alkali, than commonly used, may prove effective if given in conjunction with atropine. We have been unable to find similar studies with atropine and alkalis in the literature, although Schellong (37) reported favorable results from the use of extract of belladonna 0.01 gm. and an alkaline mixture of magnesia 0.6 gm. and bismuth subnitrate 0.2 gm.

It is of interest to compare these results with the findings of 200 experiments in which the neutralizing action of the usual Sippy powders was determined by the conventional titration method. Each of these experiments was of 24 hours duration. The results, as shown in Chart 10 are in general agreement with the pH studies. It will be noted that 90 cc. of milk and cream were least effective in reducing gastric acidity, while the improvement in neutralization coincided with the increased amounts of calcium carbonate. It is of interest to note the marked evening rise in gastric acidity despite the use of milk and cream, alkalis and atropine. Control of the night secretion

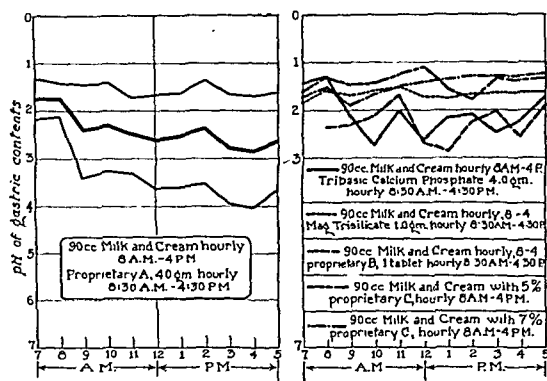


Chart 11. The effects of various proprietary preparations on the pH of the gastric contents. Proprietary A.—Tricalsate—10 experiments; Tribasic calcium phosphate—3 experiments; Magnesium Trisilicate—6 experiments; Proprietary B.—Nutrachlor—3 experiments; Proprietary C.—Casec, 5%—5 experiments, 7%—4 experiments.

is one of the difficult problems of antacid therapy. Thirty-five experiments with the Winkelstein drip revealed that this program was most effective in controlling the night acidity.

#### Other Gastric Antacids

The occasional development of alkalosis following the use of large amounts of alkali has led to the investigation of other antacids considered less likely to disturb the acid-base balance of the blood. Although the number of experiments with some of the preparations is small the results indicate that these antacids are less effective neutralizers of gastric acidity than calcium carbonate.

#### 1. Tribasic Calcium Phosphate 4.0 gm. (Chart 11)

Greenwald (38) has reported satisfactory neutralization of gastric acidity with this alkali. Shattuck and his associates (39) have confirmed the observation that this preparation acts only as a local antacid.

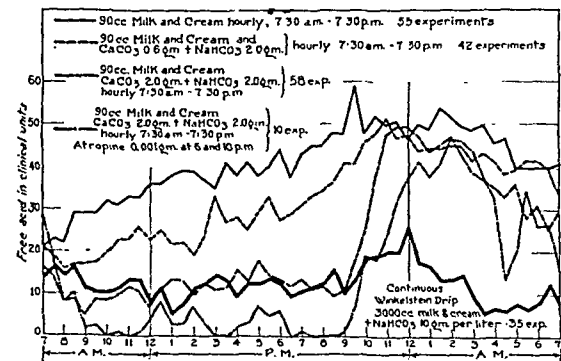


Chart 10. The effects of various neutralizing programs on the free HCl of the gastric contents (24 hour studies). The heavy line represents the influence of the continuous Winkelstein drip.

Three experiments gave the following average pH values: 1.44, 1.29 (controls) 2.14, 2.75, 2.04, 2.65, 2.18, 2.11, 2.50, 2.25, 1.78.

#### 2. Tricalsate 4.0 gm. (Chart 11)

Tricalsate is a mixture of tribasic calcium phosphate, sodium phosphate, and sodium citrate (exact formula not available). Palmer (18) has noted satisfactory reduction of the free acidity with this preparation. Ten experiments yielded the following values: 1.76, 1.76 (controls) 2.43, 2.34, 2.52, 2.65, 2.57, 2.40, 2.82, 2.88, 2.68.

#### 3. Magnesium Trisilicate (Chart 11)

This alkali has received increasing attention recently (40, 41, 42). Reid (43) found magnesium trisilicate a satisfactory substitute for the alkalies commonly employed to control gastric acidity; in the same dosage (2.0 gm.) it was slightly less prompt in neutralizing action but its effect was somewhat more prolonged. This antacid was administered in tablet form in 1.0 gm. quantities hourly in six experiments. The average pH values: 1.85, 1.59 (controls) 1.68, 1.60, 1.51, 1.71, 1.76, 1.69, 1.67, 1.66, 1.63 indicate no reduction of the gastric acidity. It should be noted, however, that Mann prescribed 3.5 gm. hourly. In two

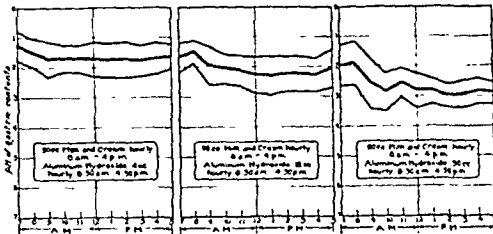


Chart 12. The effect of varying quantities of colloidal aluminum hydroxide on the pH of the gastric contents. a. 4 cc. Amounts—25 experiments; b. 16 cc. Amounts—25 experiments; c. 30 cc. Amounts—22 experiments.

preliminary experiments with powdered magnesium trisilicate the neutralizing effect was much improved. The values: 2.0 gms. = 2.92 (control) 3.49, 4.27, 3.30, 2.63, 4.09, 3.09, 2.70, 3.69, 2.10. 4.0 gms. = 1.90, 1.81 (controls) 4.81, 4.76, 2.91, 5.39, 5.30, 5.50, 4.50, 2.17, 1.88.

#### 4. Aluminum Hydroxide (Chart 12)

Aluminum hydroxide was originally introduced as an antacid in 1924. Crohn (45) was the first to investigate this antacid preparation in this country. He found that it reduced the emptying time of the stomach, lowered gastric acidity, and was devoid of untoward side effects. Einsel and his associates (46) prescribed 4-12 cc. of aluminum hydroxide one-half hour to one hour after each of six daily feedings and observed a lowering of the free acidity which returned, however, to initial levels after the medication was discontinued. Woldman and Rowland (47) found colloidal aluminum hydroxide an efficient antacid. C. R. Jones (48) reported that aluminum hydroxide given either in 4 cc. amounts three times daily or 8 cc. four times daily, completely relieved ulcer symptoms. Emery and Rutherford (49) studied the effect of colloidal aluminum hydroxide administered in the form of a constant drip and also by mouth (60 cc., after dilution three

times with water, at hourly intervals from 8 a.m. to 9 p.m.); they concluded that "it is possible to secure and maintain complete neutralization of gastric acidity if colloidal aluminum hydroxide is given in large enough amounts." Bennett and Gill (50) found that aluminum hydroxide in doses of one to three drams, possessed a neutralizing capacity as great as those of ordinary amounts of alkaline powders. In contrast to these reports, the studies of Gibson et al (27) apparently indicated that aluminum hydroxide and aluminum silicate have little neutralizing capacity. Ivy and his associates (51), after giving aluminum hydroxide cream and powdered colloidal aluminum hydroxide in large amounts daily to dogs for four months, concluded that there was no decrease in the gastric secretory response. Acid-base studies by Einsel et al and by Bennett and Gill support the claim that aluminum hydroxide, because of its amphoteric nature, does not disturb the acid base balance of the blood. The aluminum chloride formed continues to serve as an acidifying agent (approximately the strength of diluted acetic acid).

In view of these reports and the increasing clinical popularity of this antacid, a detailed study of its effect on gastric acidity was indicated. The schedule followed was the same as in preceding experiments.

A. Twenty-five experiments were performed with 4 cc. doses of aluminum hydroxide given hourly. The average pH values were: 1.27, 1.50 (controls) 1.72, 1.70, 1.70, 1.73, 1.77, 1.74, 1.78, 1.71, 1.65.

B. Twenty-five experiments with 16 cc. hourly quantities gave the following results: 1.70, 1.50 (controls) 1.96, 2.07, 2.14, 2.27, 2.31, 2.25, 2.25, 2.29, 2.08.

C. Twenty-two experiments with 30 cc. hourly amounts yielded the following average values: 1.98, 1.91 (controls) 2.57, 2.87, 2.58, 2.82, 2.84, 3.00, 2.95, 2.84, 2.92. Because of the excellent results obtained with other antacids when used in conjunction with atropine, similar studies were carried out with aluminum hydroxide.

D. Ten experiments with 4 cc. of aluminum hydroxide hourly and four 1 milligram doses of atropine daily yielded the following results: 1.50, 1.37 (controls) 1.77, 1.83, 1.93, 1.97, 2.15, 2.00, 2.00, 1.93, 1.94.

E. Two experiments with 8 cc. amounts and atropine gave the following: 1.85, 1.35 (controls) 1.86, 2.19, 2.71, 2.59, 2.56, 2.92, 2.47, 2.16, 2.54.

F. Two experiments with 16 cc. quantities and atropine resulted in: 1.31, 1.28 (controls) 1.48, 1.91, 2.17, 2.34, 2.40, 2.29, 2.16, 2.24, 1.91. These figures indicate quite clearly that the beneficial clinical effects of aluminum hydroxide are not related directly to an appreciable reduction in gastric acidity. Increasing the hourly quantities of this alkali resulted in slightly better control of the free HCl. The addition of atropine to the program likewise effected only a slight further reduction of gastric acidity, and it is even questionable, in view of the small number of experiments with atropine and aluminum hydroxide, whether these variations are statistically significant.

It is possible that the mere reduction in acidity from that of HCl to the acidity of an equimolar concentration of aluminum chloride is adequate for the protection of the diseased area.

Several *in vitro* experiments throw further light on the neutralizing action of this antacid.\*

F. The aluminum content of 1 teaspoonful (4 cc.) of the particular preparation used in the present studies was determined by dissolving in acid, precipitating with ammonia, and ashing the precipitate of aluminum hydroxide. Each 4 cc. was found to contain 0.58 gm. of aluminum hydroxide. Four cc. were added to 50 cc. of 0.150 HCl and the pH was determined electrometrically at intervals with continuous stirring of the mixture. The immediate pH was 2.20 and in 20 minutes rose to 4.0; at this level the pH remained stationary. The addition of 12 cc. more did not elevate the pH any measurable amount. It was deduced from these studies that colloidal aluminum hydroxide was slow in action and that it could never raise the pH of HCl solutions to more than 4.0 regardless of the quantity used.

A rapidly accumulating mass of evidence indicates that aluminum hydroxide has a definite place in the treatment of peptic ulcer. The mechanism of its action in relieving ulcer symptoms is probably multiple. Although the present studies show that the neutralizing influence of aluminum hydroxide is mild compared to other antacids, this preparation apparently affords a degree of protection due to its demulcent property and its considerable buffering capacity. Adams (52) mentions also the influence of colloidal aluminum hydroxide in adsorbing such toxins as histamine and histamine-like substances, on gases, and on bacteria, removing them from the ulcerated areas. The importance of this latter effect, however, in promoting the healing of ulcer while theoretically plausible, requires further clinical corroboration.

## DISCUSSION

The various antacids may be listed, on the basis of the evidence presented, as follows, in decreasing order of neutralizing capacity:

1. Calcium carbonate 4.0 gm.
2. Calcium carbonate 2.0 gm.
3. "Heavy" powders.
4. Aluminum hydroxide 30 cc.
5. "Intermediate" powders.
6. Tricalsate 4.0 gm.
7. Tribasic calcium phosphate 4.0 gm.
8. Aluminum hydroxide 16 cc.
9. "Simple" powders.
10. Sodium bicarbonate 4.0 gm.
11. Aluminum hydroxide 4 cc.
12. Magnesium trisilicate 1.0 gm.

The studies with atropine indicate that, in decreasing order of neutralizing efficiency are the following:

1. (Calcium carbonate 4.0 gm. + atropine ("Heavy" powders + atropine
2. "Simple" powders + atropine
3. Aluminum hydroxide 4 cc. + atropine
4. Atropine

It is of interest to compare these results with the theoretical neutralizing capacities of the various alkalis. These values were computed on the basis of the molecular weights of the different preparations, the quantities used, and considering 0.5% (0.143N) as the

normal value for free HCl in human gastric juice (53). The following results were obtained:

1. Calcium carbonate 4.0 gm. should neutralize 559 cc. of 0.14300 HCl.
2. "Heavy powder" should neutralize 446 cc. of 0.14300 HCl.
3. Tribasic calcium phosphate 4.0 gm. should neutralize 361 cc. of 0.14300 HCl.
4. "Intermediate powders" should neutralize 334 cc. of 0.14300 HCl.
5. Sodium bicarbonate 4.0 gm. should neutralize 333 cc. of 0.14300 HCl.
6. Calcium carbonate 2.0 gm. should neutralize 280 cc. of 0.14300 HCl.
7. "Simple powder" should neutralize 250 cc. of 0.14300 HCl.
8. Magnesium trisilicate 1.0 gm. should neutralize 192 cc. of 0.14300 HCl.
9. Aluminum hydroxide 4 cc. should neutralize 161 cc. of 0.14300 HCl.
10. Tricalsate 4.0 gm. (exact formula not available)?

The theoretical neutralizing values do not coincide with the actual results except in the case of calcium carbonate. It should be pointed out, however, that there are other important factors which determine the neutralizing effect of any antacid. These include: (a) a given quantity of alkali will not always react completely, and (b) the particular rate of reaction and limits to the reaction of an individual alkali. Calcium carbonate, for example, will react with HCl to yield a relatively neutral salt ( $\text{CaCl}_2$ ) and a weakly dissociated acid ( $\text{H}_2\text{CO}_3$ ). Tribasic calcium phosphate, on the other hand, will react slowly as follows:  $\text{Ca}_3(\text{PO}_4)_2 + 6 \text{HCl} \rightarrow 3 \text{CaCl}_2 + 2 \text{H}_3\text{PO}_4$  — the phosphoric acid reducing the pH of the gastric contents, thereby increasing the acidity. Aluminum hydroxide will react:  $\text{Al}(\text{OH})_3 + 3 \text{HCl} \rightarrow \text{AlCl}_3 + 3 \text{H}_2\text{O}$ ; since  $\text{AlCl}_3$  is an acid salt, it also will tend to increase the acidity. Magnesium trisilicate will react:  $\text{Mg}_2\text{SiO}_3 \cdot 2 \text{H}_2\text{O} + 4 \text{HCl} \rightarrow 2 \text{MgCl}_2 + 3 \text{SiO}_2 + 4 \text{H}_2\text{O}$ . The silicon dioxide produced by this reaction is without antacid properties but it may adsorb toxins, bacteria, etc., in the small bowel (52). A comparison of the results with magnesium trisilicate in tablet and in powdered form suggests that the poor results attained with the tablets are due to the fact that, in this physical form, there is inadequate interaction between the antacid and the free HCl.

The neutralizing efficiency of any antacid is dependent not only upon the chemical factors just mentioned, but also upon the continued rate of secretion of free HCl, and upon the loss of gastric contents via the pylorus (54). Keefer and Bloomfield (55) have observed that a high acid curve will be reached more quickly if gastric emptying is rapid than if the "diluent" is retained in the stomach in large quantity. One of the important factors determining the evacuation time of the stomach is the fluidity of its contents (56). In this connection, Lockwood and Chamberlin (13) noted that sodium bicarbonate (4.0 gm.), calcium carbonate (4.0 gm.), and bismuth subnitrate did not influence gastric emptying in man. Nevertheless, the superiority of calcium carbonate may be due, in part, to its relative insolubility. It is possible that the more soluble antacids are

\*We are indebted to Dr. Sidney Weinhouse of the department of chemistry for these studies.

expelled too rapidly by the stomach to allow sufficient time for neutralizing action.

There is considerable difference of opinion as to the effect of atropine on gastric secretion. Many investigators (57-65) believed that it reduced gastric acidity clinically, perhaps by the regurgitation of bile caused by relaxation of the pyloric sphincter. Bastedo (66) thought that depression of gastric secretion resulted only when untoward side effects developed. Porter's studies (67) indicated that atropine in 1 milligram doses reduced the volume of secretion obtained by histamine stimulation in man by 50 per cent; the free acidity was unchanged. Atkinson and Ivy (68) observed a slight rise in the height of titratable acidity but the diminished volume of secretion yielded a lower output of acid for the period of study. Other workers (69, 70, 71), found that not only was the total amount of secretion diminished, but also the type of secretion curve was altered. The action of atropine apparently is peripheral, on the vagal neuro-cellular junction, paralyzing the vagal nerve endings connected with Auerbach's plexus (72, 73, 74). Klee (75), Otvos (76) and Stranz (77) did not observe any constant effects of atropine on gastric emptying time. However, McCrea and MacDonald (78) found that atropine given intravenously to cats reduced intragastric pressure and decreased gastric motor activity. Lasch (79) similarly noted, in man, that atropine intravenously relieved hypertonicity and hyperperistalsis. Many investigators (62, 73, 80-83) have reported a prolongation of gastric emptying time after the administration of atropine. In this connection, we frequently noted that much larger quantities of the administered alkali were aspirated when the patients were receiving atropine as compared to the periods in which this drug was omitted.

The evidence just reviewed indicates two possible explanations for the remarkably improved neutralization which resulted when atropine was added to the alkali and milk and cream program. The reduced volume of secretion conceivably will be neutralized more effectively by a given quantity of alkali. In fact, as already shown in one patient, even smaller amounts of alkali will neutralize adequately this smaller volume of gastric secretion. The retarded gastric emptying time, furthermore, will enable the antacid to be retained in the stomach and favor more complete neutralization by allowing a longer period of interaction between the alkali and the free HCl. The results certainly indicate a distinct usefulness for atropine in ulcer therapy, particularly in those patients with a high gastric secretion.

### SUMMARY

The neutralizing influence of various commonly used antacids was investigated in a total of 290 experi-

ments performed on 25 patients with healing duodenal ulcer. The hydrogen-ion concentration of the gastric contents removed hourly was determined by the glass electrode method. Control studies were made with a general diet and with hourly feedings of a three-ounce mixture of milk and cream. The alkalis were administered hourly; they included calcium carbonate and sodium bicarbonate in varying amounts, calcium carbonate alone, aluminum hydroxide, tricalcate, tribasic calcium phosphate, and magnesium trisilicate. The effect of atropine on gastric acidity when given alone and in conjunction with various antacids, was also studied. Some of the results were compared with the results of 329 experiments in which the free HCl was determined by the usual titration method. Pertinent clinical and experimental reports are reviewed.

### CONCLUSIONS

1. The gastric acidity is slightly and temporarily reduced by the administration of food.
2. The higher the protein and fat content of the milk preparations, the greater was the neutralization of acid but, at best, this effect was not marked.
3. Of the various antacids studied, calcium carbonate in 2.0 or 4.0 gm. amounts hourly is the most effective neutralizer of gastric acidity.
4. Tricalcate, tribasic calcium phosphate and magnesium trisilicate in the dosage used are progressively less effective, in the order named, in maintaining adequate neutralization.
5. Aluminum hydroxide exerted relatively little influence on the gastric juice pH although the neutralizing capacity of 30 cc. doses was appreciable.
6. Atropine sulphate, given orally in four 1 milligram doses daily, had no influence on the pH of the gastric contents, although the volume of secretion was apparently reduced.
7. The gastric acidity was most completely controlled by the use of atropine combined with calcium carbonate or with calcium carbonate and sodium bicarbonate. The pH values obtained conform to the "proteolytic" neutralization level of Hollander. Atropine permits also the effective use of smaller amounts of alkali.
8. The effectiveness of atropine is due apparently to the resultant diminution in the volume of gastric secretion and the prolongation of gastric emptying time.
9. The influence of an antacid on the gastric acidity depends not only upon its individual neutralizing capacity, but also upon the particular chemical reaction involved, the volume of gastric secretion, and the emptying time of the stomach.

The authors wish to acknowledge the valuable assistance given by Dr. E. S. Guzman Barron during the early part of these studies.

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- absence of cells has diagnostic significance. In this connection the central problem has been to discover whether there is any definite relationship between cellular exudates in the bowel discharge and pathological change in the bowel mucosa. As a result of extensive studies, it has been established that the presence of cellular exudates in the bowel discharge indicates pathological change in the bowel wall, while the absence of cellular exudate points to bowel con-

ditions not associated with anatomical changes in the bowel wall.

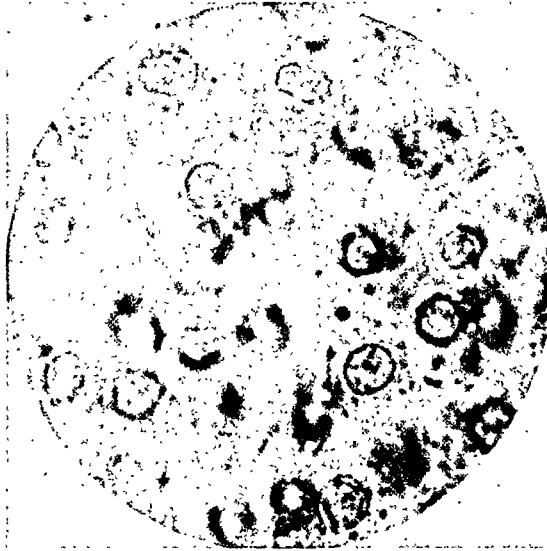
Since amebae may be found mixed in the cellular exudate of bowel discharge, it has been necessary to combine the study of amebic dysentery with that of pathological change in the bowel wall which is caused by conditions not connected with amebae. At the same time it has been necessary to attempt to develop methods for obtaining specimens which would prove adequate for the accurate study of amebae as well as for cells of other origin. It has been generally accepted that specimens which contain mucus are the best for finding the *Endameba histolytica*. This is especially true if the specimens contain mucus that is free from fecal matter and also if they are examined

immediately after they are passed, while still fresh and warm.

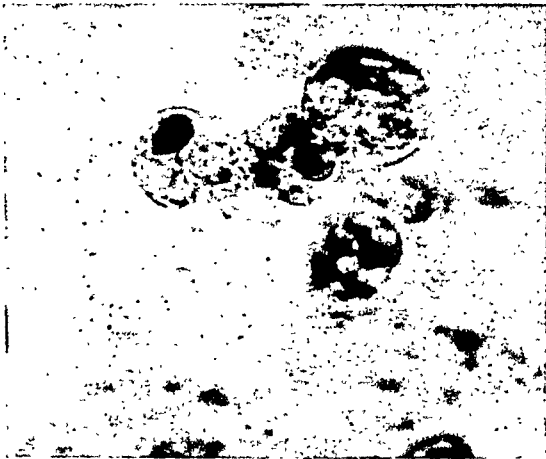
So far, the following methods have been found satisfactory for obtaining mucus specimens that would be suitable for identifying amebae as well as cells of non-parasitic origin.

The first of these methods is colonic irrigation. A colonic irrigation with tepid normal saline is continued until the return flow is entirely clear of fecal matter. The terminal mucus should be obtained for examination. In point of fact, the best specimens are those which are passed by the patient after the irrigation is completed.

The patient may be given a series of three tepid normal saline enemas. The first two should be dis-



A



B



C

Plate 1. Epithelial cells from patients with chronic ulcerative colitis. Cells stuck together as in Figs. B and C are frequently mistaken for *Endameba histolytica*. Compare with Plate 2. Methylene blue (wet coverslip preparations). Oil immersion 970x. Original photomicrographs.

carded, but the discharge following the third should be saved for examination. When it is not practicable for the patient to undergo this preparation at his office, the physician can instruct the patient to have the three saline enemas at home. He should, however, ask the patient to try to retain some of the third enema until he comes to the office, where he can evacuate it. This method of preparation makes it possible for the physician to obtain a clean specimen containing mucus which has come from the bowel wall, but without debris adhering to it. It also makes it possible

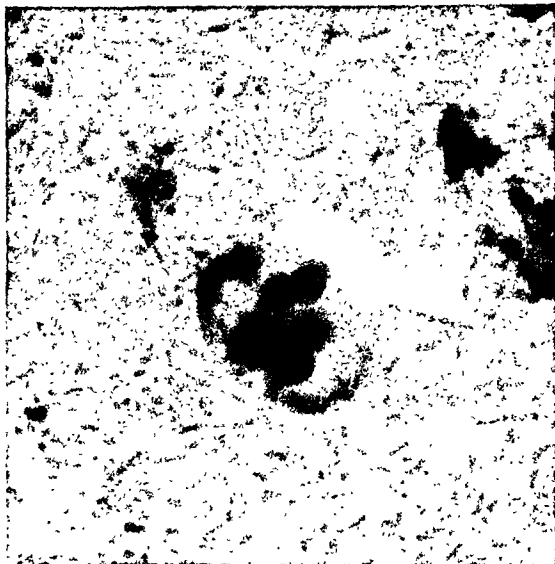
for the physician to complete a diagnosis for amebae within a day.

179 patients were prepared in accordance with these methods, and a total of 248 specimens were studied. *Endameba histolytica* was found in 14, which constituted 7.7 per cent of the total number.

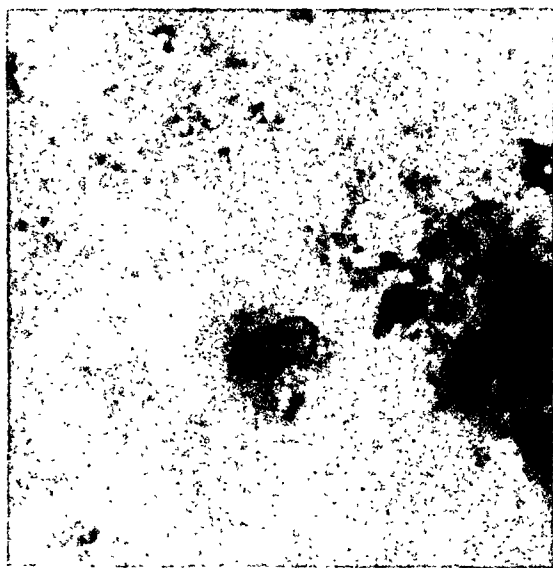
The distinct advantage of studying this type of specimen lies in the fact that, even though a cellular exudate may be present, the amebae can be readily visualized and identified. When amebae are freshly passed, they exhibit all their characteristics in tropho-



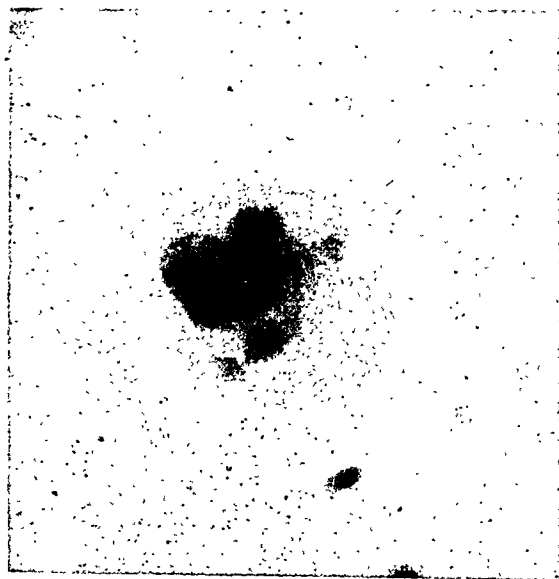
A



B



C



D

Plate 2. Trophozoites of *Endameba histolytica*. Fig. A specimen from freshly passed mucus. Unstained. Note pseudopodia, separation of ectoplasm from endoplasm and lack of nuclear detail. Figs. B, C, D preparations fixed in Schaudinn's fluid and stained with Heidenhain's iron-hematoxylin technic. Note separation of ectoplasm from endoplasm, nuclear details and ingested red blood corpuscles. Fig. D rounded out non-motile trophozoite. Oil immersion 970x (slightly enlarged) Original photomicrographs.



zoite form. When the specimen is studied with Lugol's solution, the nuclear detail of the amebae can be readily distinguished. If a cellular exudate is present and is studied with Loeffler's methylene blue, all cells except amebae will absorb the stain immediately and can be identified without difficulty.

Since amebae have characteristics which are not possessed by cells of any other type found in bowel discharges, it is of first importance for the physician to recognize them and to be able to distinguish them at all times from every other form of cellular exudate.

If confusion is to be avoided in the diagnosis of amebiasis, it is advisable to adopt a regular method of approach when preparing for the microscopic examination of specimens: (1) a saline smear, unstained, in which he may find motility of trophozoites or the size and shape of cysts. Because the nuclei do not show up in this smear, it is necessary to have (2) a smear made with Lugol's solution. The nuclear structure can be examined with this smear. If there are numerous cells in the specimen, (3) a smear with Loeffler's methylene blue will also be required. Other cells and nuclei will take up the stain immediately. If there is any suspicion that *Endameba histolytica* may be present, there should be (4) a wet smear fixed in Schaudinn's solution and stained with Heidenhain's iron-hematoxylin technique. The fixed-stain smear is of special value for permanent record, and should therefore always be available for study and for reviewing the case.

Diarrhea, which may be an important symptom in cases of infestation with *Endameba histolytica*, is also important in cases of pathological change in the bowel wall which are not associated with amebic dysentery. The relationship of diarrhea to the different types of pathological change in the bowel wall has not always been clear, and consequently has led to serious confusion in diagnosis. Furthermore the fact that it is possible to have cellular exudates independently of as well as associated with amebic infestation makes it important to establish a differential diagnosis on the basis of microscopic study of bowel discharges.

In this series of studies, Bercovitz (1) showed that in the normal individual no cells were discovered when bowel discharges were examined under the microscope, even when the specimens were watery diarrheal movements following dosage with epsom salts. It has also been shown that when cells occurred in the specimens of bowel contents obtained from seven human autopsies they were identical with the cells found in the scrapings from the bowel wall at the same location, but that they were not similar to the cells found as a result of pathological change in living persons. No cells were found in the bowel contents of three dogs which were given lethal doses of sodium amytal and were examined immediately after respiration had ceased.

When specimens from 216 patients who had various types of bowel complaint were examined, cellular exudates were found in the discharges of 142, while none were found in 73. The clinical diagnoses of that group of 142 patients included ulcerative colitis, carcinoma, diverticula, lymphopathia venereum (Frei positive), inflammation in varying degrees without ulcerations, and atrophy in varying degrees.

The purpose of this study is to give a detailed description of the cells found in the 142 patients who had positive cellular exudates in their bowel dis-

charges, and to compare them with the cells found in the scrapings from the bowel wall.

The same technique, described in detail in the first paper of this series, has been used throughout the entire study. Briefly, it includes a preliminary examination of a wet smear with methylene blue. In most instances, permanent mounts have been made by fixation in Schaudinn's fluid, and by staining with Heidenhain's iron-hematoxylin technique. These methods of staining allow for careful examination of the details of the nuclear structure, thus making possible a more accurate classification of the types of cell found.

#### TYPES OF CELL FOUND IN THE BOWEL DISCHARGES IN PATHOLOGICAL CONDITIONS

Bowel discharges from patients suffering from a great variety of pathological conditions of the bowel wall have been examined. These studies now include more than 200 patients, and in some instances the investigation has progressed to a point where it seems possible to identify with a reasonable degree of accuracy certain types of pathological change in the bowel mucosa from the types of cell found in the bowel discharges. Details of these investigations will be published when completed.

The following description of cells is based on an examination of freshly passed specimens which contain neither preservative nor stain. It will be recorded when stains or preservatives have been used.

*Large cells with prominent nuclei.* These stand out from the rest of the exudate as clearly defined cells with ectoplasm which is sufficiently sharp and heavy to be visualized readily. The size of these cells varies from 20 to 30 microns to as much as 150 microns. The average, however, is from 20 to 40 microns. Their shape is usually oval, round or regular. No protrusions of any sort have been seen. Motility has not been observed at all, although occasionally what seemed to be a change in shape has been noticed. But this change could not be entirely differentiated from the influence of fluid currents under the coverslip. Nothing suggestive of progressive motility has ever been observed. The endoplasm may be either smooth, very finely granular, or else it may contain coarse granules. In some instances there are definite vacuoles, while especially large cells seem to have the most marked tendency towards vacuolization. At the present time it is not possible to state what influences cause the changes in the character of the cytoplasm of these cells.

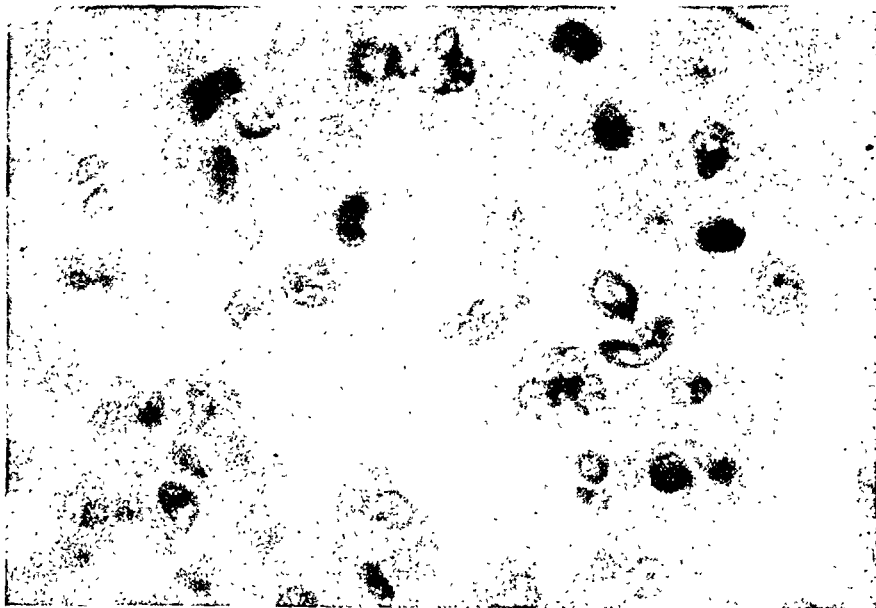
In the fresh unstained preparation under the coverslip the nucleus is prominent and is easily visualized. It is so definite that it can be distinguished even with the high dry objective, using the 10x eyepiece. At times the nucleus appears to be granular and composed of many fine or of relatively coarse granules packed into a compact mass. More commonly there is a distinct nuclear membrane which is usually relatively heavy and solid, although at times it may appear to have a distinct beading composed of coarse bits of chromatin matter. The karyosome is usually large, heavy, and easily visualized, and it may be situated either centrally or eccentrically. In the fresh, unstained preparation the nucleus often has the appearance of a ring, similar to the so-called ring nuclei which are observed in bacillary dysentery. These

characteristics are also brought out when the methylene blue preparation is used.

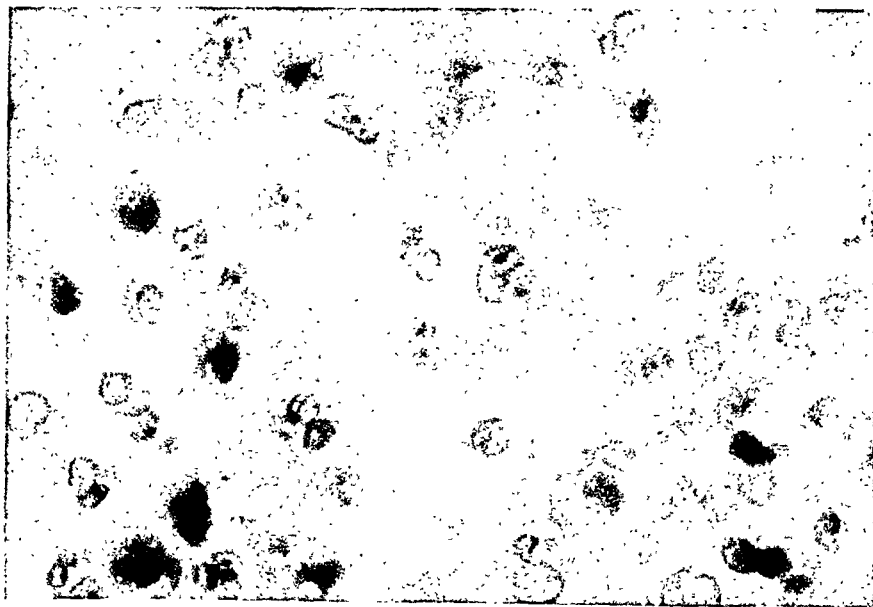
In specimens which have been fixed in Schaudinn's fluid and stained as wet preparations with Heidenhain's iron-hematoxylin, such as is used for the staining of intestinal protozoa, the nucleus most frequently appears as a ring. It is prominent in the cell, and the nuclear membrane is quite solid, although it may appear irregular and even beaded when examined under

a powerful light. The karyosome is prominent and not infrequently fine hair lines of chromatin matter may appear to pass between the karyosome and the nuclear membrane. In these cases the nucleus is clear except for this distribution of chromatin matter just noted. In other instances the karyosome does not appear as a solid mass, but divided; it may even be fragmented.

These cells also occur when there is a heavy cellular exudate of other types. They are numerous enough to



A



B

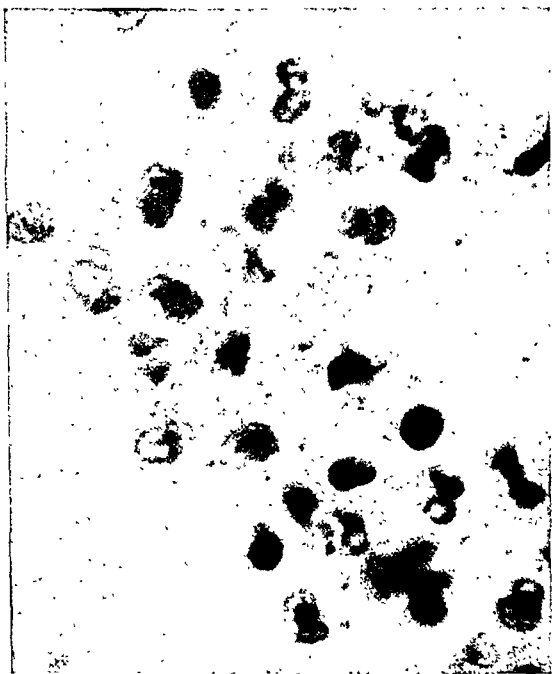
Plate 3. Polymorphonuclear leucocytes in cellular exudates from patients with Chronic Ulcerative Colitis. Note tendency to "ringed nuclei." Compare plate showing solid nuclei. Heidenhain's iron-hematoxylin stain. Oil immersion 970x. Original photomicrographs.



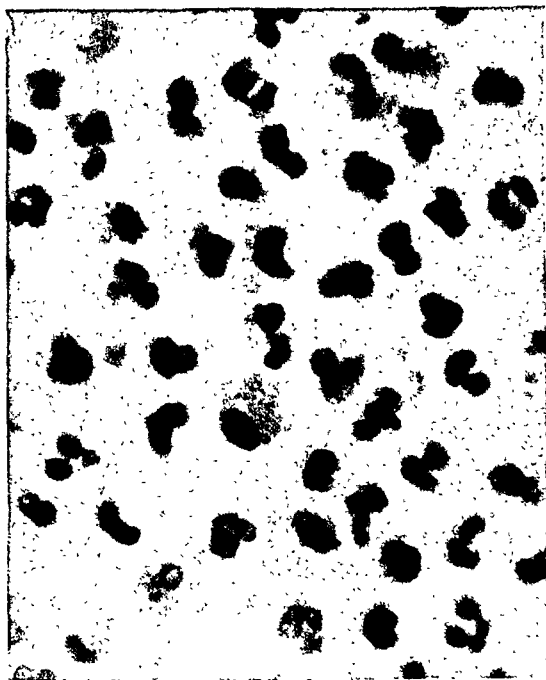
A



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Plate 4. Polymorphonuclear leucocytes in cellular exudates from patients with chronic ulcerative colitis. Note tendency to solid nuclei. Heidenhain's iron-hematoxylin stain. Oil immersion 970x. Original photomicrographs.

be seen readily in wet preparations, even though they do not constitute the major portion of the cells in the exudate. It is most important that they should not be confused with *Endameba histolytica*. The chief characteristics by which the *Endameba histolytica* may be identified include size, which may be up to 20 microns in the trophozoite forms; progressive motility with the formation of definite pseudopodia, and differentiation between endoplasm and ectoplasm. The pseudopodia of the ectoplasm take part in the progressive motility, but when this occurs, the endoplasm does not enter the pseudopodia. The cytoplasm is usually finely granular, although it may be vacuolated; it contains ingested red blood cells, but no bacteria or other particles. The nucleus of the *Endameba histolytica* is difficult to visualize in the fresh, unstained preparation, but when it is fixed in warm Schaudinn's fluid and stained with Heidenhain's iron-hematoxylin technique, it appears to be open with fine beading of the nuclear membrane and a delicate centrally placed karyosome. The *Endameba histolytica* has the same characteristics in the encysted form, although the nuclei may be one, two or four in number, bipolar in their distribution within the cyst, and at times it may be possible to demonstrate a chromatoid body with blunt rounded ends. The *Endameba histolytica* occurs also with a scant cellular exudate. But before a cell can be identified as *Endameba histolytica*, it must possess all these characteristics. If there is a heavy cellular exudate containing numerous cells which show one or more of the characteristics of this protozoa, those cells must be viewed with suspicion until one which is typical in all respects is demonstrated in the fixed stained preparations.

Exudates containing these large cells with prominent nuclei may be fixed in formalin, embedded in paraffin, sectioned and stained with the usual pathological technique, using Delafield's hematoxylin and eosin. When this procedure is followed, the nuclei become more solid and do not show the same characteristics as in the fresh or wet-fixed preparations.

*Polymorphonuclear leucocytes* are readily seen in the exudates of the bowel discharges. In the fresh, unstained preparations the nuclei appear as open rings, and there are usually two or three such nuclear rings in a single cell. Unfortunately, these cells have been confused with cystic forms of *Endameba histolytica* when the fresh, unstained preparations have been used.

In order to differentiate between the two forms, it should be noted that the nuclei of the cysts of *Endameba histolytica* are not readily visualized in the fresh, unstained preparation. The chromatoid bars, characteristic of the *Endameba histolytica* cyst, may be visualized when unstained, but the nuclei cannot. If two or three prominent nuclei are present, it is probable that the cells are polymorphonuclear leucocytes, and the specimen should be re-examined, using for this purpose Loeffler's methylene blue. In this type of preparation the nuclei of the leucocytes may be solid or may have open rings in which there is beading of the nuclear membrane. Heavy granules of varying sizes and shapes are found, both within the nucleus and in the cytoplasm. It is also possible by this method to determine whether the polymorphonuclear leucocytes are segmented or whether they are young forms. Whenever there is any suspicion that cysts of protozoa

may be present, Lugol's solution should be used in order to bring out the nuclear structure. The characteristic nuclear structure of the *Endameba histolytica* cyst is not present in the polymorphonuclear leucocytes. As the risk of error is so great, the presence of encysted forms of protozoa should not be determined on a basis of the nuclear contents observed in the fresh, unstained preparation.

*Epithelial cells* are frequently found in bowel discharges. Methylene blue preparations are the simplest to use for the observation of these cells. As a rule they appear to be of different sizes and shapes, and have nuclei which are generally round or oval, solid or ringed. In some cases, the methylene blue stain appears like a solid mass, while in others, it has the appearance of an open ring with fine beading. The cytoplasm is usually quite smooth, finely granular, and it may or may not have coarse masses of varying shapes. These cells are entirely different from the large cells with prominent nuclei and from the polymorphonuclear leucocytes.

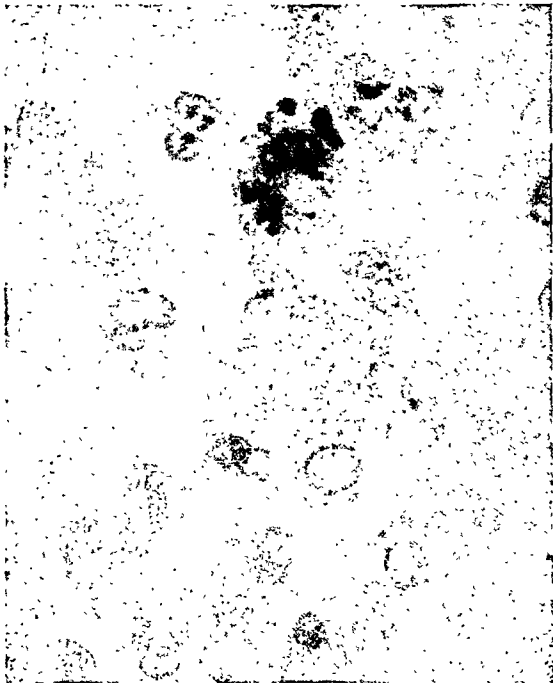
When the cells found in the scrapings of the bowel wall are compared with those found in the bowel discharges of patients who complain of symptoms referable to the gastro-intestinal tract, it becomes clearly evident that they are entirely dissimilar. In point of fact, cells have not been found at any time in the scrapings from the bowel wall which even simulated those found in the discharges of patients with bowel complaints. On rare occasions, cells have been found in the bowel discharges of patients with symptomatology that simulated those found in the scrapings.

In their final report Wenyon and O'Connor state "the pus and other cells are probably exudate cells derived from the outpouring of liquid from lymphatics and blood vessels; while the latter (elongated cells changed and distorted in various ways are evidently derived from the columnar cells of the gut wall itself) are exfoliations from the gut wall." These authors suggested also that the cellular exudate studies which they had carried on in the differentiation of amebic and bacillary dysentery might be applied to other conditions of the bowel. The studies herewith reported confirm entirely the previous work done and also the suggestion of Wenyon and O'Connor as to the diagnostic significance of cellular exudate studies on bowel conditions.

## SUMMARY

During the past four years, studies in the cellular exudates of bowel discharges have established that the presence of cellular exudates in the bowel discharge indicates pathological change in the bowel wall, while the absence of cellular exudate points to bowel conditions not associated with anatomical changes in the bowel wall.

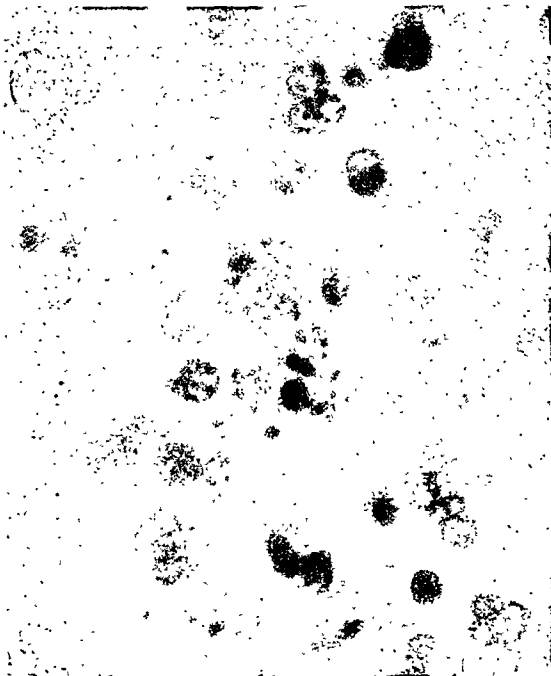
The bowel discharges of patients suffering from various pathological conditions of the bowel contain three well-defined types of cell which may be readily identified. These types include (1) large cells with prominent nuclei. These cells have a clearly defined ectoplasm. The nuclei have a definite nuclear structure which at times is beaded with either delicate or heavy granules of chromatin matter. While these cells are entirely different from the *Endameba histolytica*, they are frequently confused with them and as a result a



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B



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Plate 5. Bacillary dysentery (Flexner) exudates showing cells which might be confused with *Endameba histolytica*. Oil immersion 970 x. Figs. A, B, C methylene blue wet coverslip preparations. Fig. D formalin fixation, paraffin section H & E stain. Original photomicrographs.

mistake is made in the diagnosis and treatment of the patient. (2) Polymorphonuclear leucocytes which, in the wet stained preparation, may or may not have open ringed nuclei or solid nuclei similar to those seen in the methylene blue. Those which have open ringed and beaded nuclei are frequently mistaken for cysts of amebae. However, these may be differentiated by a careful study of the specimens. (3) Epithelial cells of various sizes and shapes are found. With the methylene blue preparation, these may be readily demonstrated.

No cells of any of these types have been found in any autopsy specimens that have been examined. They are characteristic of pathological change in the bowel wall. Studies are now in progress in which an attempt is being made to arrive at a provisional diagnosis of

the type of pathological change in the bowel mucosa from the type of the cellular exudates. The results of these studies will be made available in the near future.

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## Hypoglycemic Reactions From Protamine Zinc Insulin\*

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**P**ROTAMINE insulin was introduced with the expectation of more evenly controlled blood sugars and comparative freedom from insulin shock. In most patients this hope has been realized, but recently there have been numerous reports of difficulty in regulating certain cases, and of reactions from protamine zinc insulin, which are more severe and more difficult to relieve than those from regular insulin (1, 2, 3). From known diabetics entering the hospital we hear frequently that protamine insulin has been tried and given up as unsatisfactory. In some of these cases severe reactions occurred only during the period of transition from regular to protamine zinc insulin. Even a single reaction if severe enough may discourage both patient and physician from further use of protamine zinc insulin, whereas greater familiarity with its proper use and more careful supervision might have produced satisfactory results.

Like others (2, 4, 5), we have had patients who could not be controlled satisfactorily with protamine zinc insulin. In a few patients protamine zinc insulin seems not to be as effective as regular insulin. Several patients have been found to be more allergic to protamine zinc insulin. A small number of patients who expected freedom from insulin shock with protamine zinc insulin have been disappointed and encountered reactions which were more severe than with regular insulin.

Somogyi (6) has called attention to the unfavorable effect of hypoglycemic shock on the course of diabetes and the disturbance (7) it brings about in the delicate and intricate mechanism of glucose distribution in the body, which is not immediately restored by the administration of glucose. With the realization of the

danger and ill effects of hypoglycemia it was decided to make a survey of patients who had taken both regular and protamine zinc insulin and compare the results.

The survey included 89 persons who had taken both kinds of insulin. None were included who had taken protamine zinc insulin for less than 6 months. Forty-three of the 89 patients (48.3%) had no reactions from either regular or protamine zinc insulin (Table I). While taking regular insulin 42 patients (47.5%)

TABLE I.  
*Frequency of insulin shock with regular and protamine insulin*

	Number of Patients
Total number of patients	89
No shock	43
Shock from regular insulin	42
Shock from protamine	32
Shock from regular and not from protamine	14
Shock from protamine and not from regular	4

were subject to hypoglycemic reactions. After the shift to protamine zinc insulin 32 patients (36%) encountered reactions. Fourteen patients (15.7%) had no reactions after being shifted from regular to protamine zinc insulin. Four patients who had been free from reactions on regular insulin complained of hypoglycemic symptoms with protamine zinc insulin.

Of the 28 patients who encountered reactions from both protamine and regular insulin, 21 (75%) observed less frequent reactions with protamine zinc

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insulin (Table II). Two patients had more frequent reactions with protamine zinc insulin.

Decreased severity of reactions with protamine zinc insulin was noted by 19 patients (60.7%). Four patients (17.8%) stated that hypoglycemic symptoms were more severe with protamine zinc insulin than they had experienced with regular insulin.

TABLE II

*Relative frequency and severity of reactions from regular and protamine insulin*

	Number of Patients
Patients having reactions from both insulins	28
Less frequent reactions with protamine	21
More frequent reactions with protamine	2
No difference in frequency	5
Less severe reactions from protamine	19
More severe reactions from protamine	4
No difference in severity	5

The age of the patients studied varied from 17 to 75 years. No child diabetics were included. Table III indicates the number of patients by decades and the percentages in each decade which had hypoglycemic reactions while taking regular and protamine zinc insulin. In each age group, fewer patients had reactions from protamine zinc insulin than from regular insulin. Age does not seem to affect significantly the frequency of hypoglycemic reactions.

The length of time the patients had had diabetes varied from 1 year to 30 years (Table IV). No sig-

TABLE III

*Age of patients and frequency of insulin shock*

Age	Number of Patients	Number of Patients Having Reactions	
		With Regular Insulin	With Protamine
11-20 yrs.	2	1 (50%)	0
21-30 yrs.	9	7 (77.7%)	5 (55.5%)
31-40 yrs.	10	8 (80%)	6 (60%)
41-50 yrs.	26	12 (46%)	11 (42.3%)
51-60 yrs.	24	7 (29%)	5 (20.8%)
61-70 yrs.	15	5 (33.3%)	5 (33.3%)
71-80 yrs.	3	2 (66.6%)	0
Total	89	42 (47.1%)	32 (35.9%)

nificant relationship was noted between the duration of diabetes and the frequency of hypoglycemic reactions from either regular or protamine zinc insulin.

As might be anticipated, insulin reactions were much more frequent in the undernourished (Table V). Twenty-three patients were more than 11% below their estimated normal weight. Of these, 15 (65.2%) had reactions with regular insulin and 13 (56.5%) with protamine zinc insulin. There were 34 patients in a group between their normal weight and 10% below normal which level has been considered the

optimum for control of diabetes. In this group of 34 insulin reactions were slightly less frequent. Nineteen patients (55.9%) experienced reactions from regular insulin and 15 (44.1%) from protamine zinc insulin. It is significant to note that of the 32 patients who were above their estimated normal weight, 8 (25%) experienced reactions from regular insulin and only 4 (12.5%) from protamine zinc insulin. The striking decrease in frequency of reactions with over-nutrition is more pronounced with protamine zinc insulin than with regular insulin.

Since hypoglycemic reactions represent the most frequent and difficult problem (4) in the management

TABLE IV

*Duration of diabetes and frequency of insulin shock*

Duration of Diabetes	Number of Patients	Number of Patients Having Reactions	
		With Regular Insulin	With Protamine
1-4 yrs.	29	8 (27.5%)	8 (27.5%)
5-8 yrs.	25	14 (56%)	9 (36%)
9-12 yrs.	12	4 (33.3%)	3 (25%)
13-16 yrs.	17	13 (76.4%)	12 (70.6%)
17 plus	6	3 (50%)	0
Total	89	42	32

of diabetics using protamine zinc insulin, the following question is raised. In order to take advantage of the lowered frequency of insulin shock among the better nourished diabetic patients, would it not be justifiable and advisable to permit a higher level of nutrition than has been considered optimum in the past? A favorable effect on the incidence of tuberculosis and other infections might reasonably be expected by maintaining diabetics at least at their normal weight unless they are very old.

The amount of actual carbohydrate in the diet varied from 100 grams per day to 400 per day (Table VI). The majority of patients were given from 150 to 200 grams per day. Larger amounts were necessary for those whose occupation required a high caloric intake and who were inclined to be undernourished.

No significant relationship was established between the amount of carbohydrate in the diet and the frequency of insulin reactions. Reactions were less frequent among the patients taking lower carbohydrate diets but this group represents patients who were better nourished and taking less violent exercise. Four

TABLE V

*State of nutrition and frequency of insulin shock*

Per Cent Above or Below Normal Weight	Number of Patients	Number of Patients Having Reactions	
		With Regular Insulin	With Protamine
0 to -10%	34	19 (55.9%)	15 (44.1%)
-11% and less	23	15 (65.2%)	13 (56.5%)
Above normal	32	8 (25%)	4 (12.5%)

hundred grams of carbohydrate and a total caloric intake of 5000 calories were necessary for satisfactory control in one patient, a hard working farm hand.

In the groups taking larger amounts of carbohydrate, reactions were more frequent but it is probable that this increased frequency was due not to the diet but to greater and perhaps more variable physical exercise and to the undernutrition which made the higher carbohydrate allowance necessary.

TABLE VI

*Carbohydrate in diet and frequency of insulin shock*

Carbohydrate in Diet	Number of Patients	Number of Patients Having Reactions	
		With Regular Insulin	With Protamine
100 gm.	6	1	0
101 to 150 gm.	34	16	13
151 to 200 gm.	39	19	15
201 to 250 gm.	7	4	4
251 to 300 gm.	2	1	0
400 gm.	1	1	0

Insulin reactions were encountered more frequently when higher doses of insulin were necessary for adequate control of the disease (Table VII). This was true for both regular and protamine zinc insulin although reactions were less frequent with protamine zinc insulin at all levels. In the group of 30 patients receiving 20 units or less per day, 9 (33.3%) had reactions with regular insulin and 6 (20%) with protamine zinc insulin. There were 46 patients who received from 21 to 40 units of insulin per day. Of these, 24 (52%) encountered hypoglycemic reactions from regular insulin and 19 (41.3%) from protamine zinc insulin. Reactions were still more frequent in patients who required more than 40 units of insulin

TABLE VII

*24 hour insulin dosage and frequency of insulin reactions*

Insulin Dosage	Number of Patients	Number of Patients Having Reactions	
		With Regular Insulin	With Protamine
20 units and less	30	9 (33.3%)	6 (20%)
21-40 units	46	24 (52%)	19 (41.3%)
More than 40 units	13	9 (69%)	7 (53.8%)
Total	89	42	32

daily. With protamine zinc insulin reactions increased in frequency with the increased dosage but to a less extent than with regular insulin. Nine (69%) of the 13 patients who took more than 40 units of regular insulin had reactions and 7 (53.8%) from protamine zinc insulin.

Most patients could be controlled with a single daily injection of protamine zinc insulin (Table VIII). Patients who could not be controlled with one dose

were given additional injections either of protamine zinc insulin or of regular insulin. Patients in this latter group, which of course consisted of the more severe diabetics, had a higher incidence of reactions and were not as satisfactorily controlled as those in whom a single dose was sufficient. Fifty units of protamine zinc insulin seems to be the maximum dose to use safely and efficiently in one injection.

Seventy-five patients were satisfactorily controlled by 1 dose of protamine zinc insulin daily. Twenty-one of these patients (28%) were subject to reactions. Two doses of protamine zinc insulin per day were required by 19 patients and 9 of these patients (47.3%) reported reactions. Three patients were given 1 dose of protamine zinc insulin and a simultaneous dose of regular insulin daily. Two of these patients had reactions. Two patients required 2 doses (morning and evening) of protamine zinc insulin and a supplementary dose of regular insulin which was given at the same time as the morning dose of protamine zinc insulin. Both of these patients experienced reactions.

Hypoglycemia from protamine zinc insulin develops very slowly. Symptoms may not occur until an extremely low blood sugar level has been reached and has been present for considerable time. Blood sugars

TABLE VIII

*Number of doses of protamine insulin and frequency of reactions*

Number of Doses	Number of Patients	Number of Reactions	Per Cent
1 of protamine	75	21	28
2 of protamine	19	9	47.3
1 of protamine and 1 of regular	3	2	66.6
2 of protamine and 1 of regular	2	2	100

as low as 30 mgm. were reported in bed patients who nevertheless were entirely free of hypoglycemic symptoms. When protamine zinc insulin is given before breakfast reactions occur most frequently in the early morning hours, the next day, or just before breakfast (especially if breakfast is delayed).

Reactions due to exercise (especially unusual exercise) are more apt to occur with protamine zinc insulin than with regular insulin. Delayed meals or failure to absorb food from the gastro-intestinal tract may cause hypoglycemia with protamine zinc insulin just as with regular insulin.

Patients familiar with hypoglycemic reactions resulting from regular insulin may misinterpret the symptoms of hypoglycemia due to protamine zinc insulin the first time they occur. This is due to the insidious development and changed character of the reaction. Hypoglycemia progresses to a lower level and more alarming symptoms occur which require more than the usual amount of glucose for relief. Protamine zinc insulin shock tends to recur within an hour or two after the first symptoms have been relieved, and patients should be informed of this fact.

Protamine zinc insulin reactions develop so much more slowly than reactions from regular insulin that



there is ample time for their relief by glucose if they are recognized. To aid ourselves and our patients to recognize the early stages of a reaction, we have tabulated the symptoms which occur most frequently during protamine zinc insulin shock in 43 patients who were subject to them. These are shown in Table IX in the order of their frequency.

A majority of the patients listed the same 4 or 5 symptoms. It will be noted that nervousness and trembling (a sensation of trembling in the epigastric region) and weakness were the most common symptoms, and occurred in 29 patients (67.4%). Twenty-three patients (53.5%) complained of hunger. Sweating was noted in 21 instances (48.8%) and is a valuable objective sign which may enable another person to suspect the true state. Blurring of vision also occurred in 21 cases (48.8%). Nineteen patients (44.4%)

TABLE IX

*Frequency of various hypoglycemia symptoms in 43 patients reporting reactions from protamine zinc insulin*

	Number of Patients	%
1. Nervousness and trembling	29	67.4
2. Weakness	29	67.4
3. Hunger	23	53.5
4. Sweating	21	48.8
5. Blurring of vision	21	48.8
6. Headache	19	44.4
7. Faint feeling	19	44.4
8. Somnolence	13	30.2
9. Dizziness	13	30.2
10. Nausea	8	18.6
11. Parasthesias	7	16.3
12. Disorientation	6	
13. Coma	5	
14. No subjective symptoms (diagnosis by wife)	1	
15. Hemiplegia (transitory without loss of consciousness and relieved by glucose)	1	

reported headache and the same number complained of feeling faint. Somnolence and dizziness were noted by 13 patients (30.2%); 8 patients (18.6%) experienced nausea. Parasthesias were observed by 7 (16.3%). In 6 patients hypoglycemia progressed to the point where there was disorientation and in 5 to the point of loss of consciousness. One patient has had two attacks of transitory hemiplegia.

Disorientation is obviously a dangerous complication and fortunately does not develop often unless early symptoms are neglected. One patient, a schoolteacher, had noticed hunger and weakness in the early afternoon and dismissed these symptoms as not being due to hypoglycemia. Later she heard herself saying things which did not sound "right" to her own ears. She stated this alarmed her at first but soon she did not care if her statements sounded right or not. She finished her afternoon of teaching and was driven home by a fellow teacher. On her arrival home she made no reply to her mother's greeting but went to

sleep on the sofa. In a short time she could not be aroused. Orange juice restored her promptly.

A second instance of disorientation developed when the warning symptoms were not heeded. This patient, a male, was employed in a large factory. Several hours after lunch he correctly interpreted weakness and sweating as due to hypoglycemia and started for the factory lunch wagon as he had no carbohydrate with him. Before he arrived he forgot what he was going for and where he was going. His unusual actions finally caused him to be taken to the first aid station where his condition was correctly diagnosed and treated.

In a third case of disorientation and coma, alcohol apparently was a contributing factor. On a holiday this patient took a generous quantity of whiskey and neglected to eat his lunch on time. Doubtless the symptoms which might have warned him of hypoglycemia were attributed to alcohol. His queer actions likewise were considered by his family as alcoholic until he lapsed into coma from which he could not be aroused. Later, glucose administration revived him.

Insulin reactions as disturbing as these just described have occurred with regular insulin and it has been gratifying to note that two of our patients, subject to coma without warning while using regular insulin, could recognize early symptoms of hypoglycemia due to protamine zinc insulin before the state of disorientation or coma was reached. A young man who had given up driving his car because of attacks of sudden hypoglycemic coma which had resulted in several accidents has had no severe hypoglycemic shocks since he was regulated with protamine zinc insulin. Oddly enough, he is now employed as a truck driver.

The other patient, a woman of 45, had severe diabetes which had never been satisfactorily controlled with regular insulin over a period of fifteen years. During this time she had been subject to severe hypoglycemic reactions which occurred without warning symptoms. The reactions began with disorientation of variable duration during which the patient knew there was something wrong but rarely attributed the condition to hypoglycemia. Unless help was available from her family the patient lapsed into coma in which there were choreiform movements and outbursts of hysterical crying. After a carefully supervised transition period this patient's diabetes was found to be much better controlled on one dose of protamine zinc insulin with a small dose of regular insulin given at the same time. A few reactions have occurred at long intervals and these have been mild because the patient is warned of the protamine zinc insulin hypoglycemia by a feeling of nervous excitement which she has learned to interpret correctly and to treat.

Transitory hemiplegia, involving the arm, leg, and face accompanied hypoglycemia on two occasions in one patient. This condition, a rare complication, has been described as a result of hypoglycemia from regular insulin (8, 9). Our patient was a man, 37 years of age, who had a moderately severe diabetes which required 70 units of protamine zinc insulin daily for control. An unusual grade of peripheral arteriosclerosis was present. Both attacks occurred in the morning, and were discovered when the patient fell while rising from his bed. There was no loss of

consciousness, convulsion, or speech disturbance. Complete and prompt recovery from each attack followed the taking of orange juice.

Hypoglycemic symptoms vary greatly in different patients but in each patient reactions seem to reproduce the same *chain* of symptoms. Table X indicates the initial or warning symptom by which individual patients have been able to recognize hypoglycemia. Eleven of the 43 patients reported nervousness or a sensation of trembling as the earliest warning symptom. Sweating was noted as the first symptom by 8 patients, weakness by 5, and hunger by 5. Three patients were warned of impending hypoglycemia by nausea. Headache was the first symptom of 2 patients and a feeling of faintness by 2 others.

In two patients who had early morning hypoglycemia, the condition was discovered by their failure to waken in the morning at the usual time. For one patient a numb feeling around the mouth proved a re-

TABLE X

*Initial symptom of hypoglycemia in 43 cases reporting reactions from protamine zinc insulin*

	Number of Patients
1. Nervousness and trembling	11
2. Sweating	8
3. Weakness	5
4. Hunger	5
5. Nausea	3
6. Headache	2
7. Faint feeling	2
8. Failure to wake	2
9. Parasthesias (of face)	1
10. Dizziness	1
11. Change in appearance noticed by wife	1

liable warning. Dizziness was the first symptom of one patient. A watchful wife who interpreted a mask-like face was able to keep her diabetic husband from having severe reactions in another instance.

## DISCUSSION

The introduction of protamine zinc insulin has made the satisfactory control of the diabetic better but more complicated. New criteria for the recognition of the slowly developing hypoglycemia must become more generally known if the best management is to be accomplished. The time of the expected reactions is shifted from the two to four hour period after injection to a period sixteen to twenty-four hours after injection.

Exercise has come to be a more important factor in the production of hypoglycemia. Patients using protamine zinc insulin are more prone to have hypoglycemia as a result of exercise than are patients using regular insulin. Such reactions often occur when the patient is taking more than his usual exercise. Patients who can anticipate increased exercise on certain days or weekends should be warned of the probability of reactions. They should supply themselves with port-

able carbohydrate to treat a reaction and a recurrence of it should this happen. Patients who have reactions regularly on weekends should take an additional carbohydrate meal preceding exercise. Reduction in dosage on the day of exercise is not feasible because of the cumulative effect of protamine zinc insulin.

Regularity of meals is of greater importance with protamine zinc insulin than with regular insulin and a delayed meal may permit a reaction to occur.

Rapidly absorbable carbohydrate and slow acting protamine zinc insulin do not form an ideal combination since not enough insulin is available for rapid oxidation of the meal. Further, between meals there may be periods during which there is not enough glucose available to cover the insulin which is constantly being absorbed and the blood sugar may be lowered too far. This uneven matching of available glucose and available insulin can be offset to some extent by giving an extra meal in the evening. Carbohydrate absorption may be delayed and prolonged to some extent by avoiding the monosaccharids or by taking cream or other fat with them.

The partitioning of meals so that the largest meal precedes the longest period without food may be useful. This is particularly so if the protein is divided to provide a larger amount at the evening meal. By this method, protein which is more slowly digested and absorbed than carbohydrate, will provide small amounts of glucose over a considerable period of time through the gradual deamination of amino acids. This plan which was suggested by Pollack and Dolger (10) is a rational one for providing a steady small supply of glucose to match the slow absorption of protamine zinc insulin.

Because of the delayed effect of protamine zinc insulin a better control is maintained by dividing the diet into at least four feedings, the last of these to be given at 10:00 p.m. This plan quite effectively prevents early morning reactions. Various proportional divisions of the food intake have been tried. Some authors recommend the diet to be divided into one-sixth, two-sixths, two-sixths, one-sixth and others recommend a division of 20%, 35%, 35%, and 10%, for breakfast, lunch, dinner and bed time respectively. We follow the latter plan and have found it very satisfactory.

In changing a patient who has been using regular insulin to protamine zinc insulin, the following plan seems to provide an interim period free from hyperglycemia. On the first day four-fifths of the total daily regular insulin dose is administered as protamine zinc insulin. If three doses of regular insulin have been used the first two doses are given as usual but only half of the third dose is given. On the second day the same dose of protamine zinc insulin is given and the full first dose of regular insulin but the noon dose is halved and the last dose omitted. On the third day the same amount of protamine zinc insulin is administered; the breakfast dose of regular insulin is halved and the lunch and supper insulin omitted. On the fourth day protamine zinc insulin alone is administered. Readjustment of this dose may be necessary on subsequent days. In our experience fewer units of protamine zinc insulin were required for adequate control than were necessary when regular

insulin was used. Table XI gives this data in tabular form:

It is not unfortunate if a patient has a mild insulin reaction during hospitalization so he may be taught to recognize the warning signals of hypoglycemia. Every new patient should be instructed not to disregard mild symptoms but to consider them as possible hypoglycemic manifestations. In our experience nervousness, a trembling sensation, sweating, weakness, hunger, nausea and headache are the most common early symptoms and call for a trial administration of glucose for relief. Nausea is a particularly disturbing symptom with protamine zinc insulin. It should bring to mind the possibility of abdominal complications. It

TABLE XI

*Plan for substituting protamine zinc insulin for regular insulin*

Regular Insulin Dose	Protamine Zinc Insulin			
	1st Day	2nd Day	3rd Day	4th Day
Breakfast 20	48 protamine 20 regular	48 protamine 20 regular	48 protamine 10 regular	48 protamine
Lunch 20	20 regular	10 regular	0	0
Supper 20	10 regular	0	0	0

may represent a symptom of hypoglycemia already present. It may hinder absorption of ingested glucose making intravenous therapy obligatory. If the nausea is prolonged beyond the next meal, the possibility of later hypoglycemia should be borne in mind. If nausea is present and glucose by mouth does not relieve symptoms, hypoglycemia cannot be excluded by this fact alone.

The masking of hypoglycemic symptoms by alcohol has happened in only one of our patients and no serious result followed. The dangerous possibilities from this combination can be readily imagined and if patients persist in using alcohol, they should be

warned of the possibility of unrecognized insulin reactions and of the still greater danger if food is delayed.

In our experience the most severe reaction is the first one. After this the patient learns to recognize warning symptoms and because of the slow development of hypoglycemia has ample time to treat them with glucose.

Protamine zinc insulin reactions represent the most difficult problem in its administration. By proper education and strict supervision at the beginning of treatment much can be accomplished toward their prevention, early recognition and proper treatment.

### SUMMARY

1. A study was made of hypoglycemic reactions in 89 patients who had taken both regular and protamine zinc insulin for at least 6 months.
2. Fewer reactions occurred with protamine zinc insulin than with regular insulin.
3. Patients who had reactions with protamine zinc insulin reported them in general to be less severe and less frequent than with regular insulin.
4. Patients who were overweight were relatively free from reactions with protamine zinc insulin.
5. Hypoglycemic symptoms from protamine zinc insulin as described by 43 patients were listed in the order of their frequency.
6. Initial or warning symptoms of protamine zinc insulin shock were given in the order of frequency.
7. The prevention, recognition and treatment of protamine zinc insulin hypoglycemia were discussed.

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## The Bactericidal Action of Metallic Ions in Broth Containing Dehydrated Apple

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THE treatment of diarrhea, especially in children, by means of raw apple pulp was first reported by Heisler (1) and Moro (2). Since then many workers have reported on the use of raw apple, dehydrated apple, agar pectin and pectin. Raw apple is not always obtainable and because of this, dehydrated apple is often used in its place. There are those who believe that the therapeutic action of the apple lies in its pectin content and therefore use pectin or agar-pectin

mixtures instead. Other workers believe that pectin is only a part of the active complex. Frank (3) compared apple powder with pectin in four day clinical trials and found that apple powder cured diarrhea in 83 per cent of the cases while pectin produced cures in only 16 per cent. Malyoth (4) states that while pectin is the primary factor responsible for the effectiveness of the apple diet, other substances besides pectin are beneficial and serve as an aid to it. He further believes that it is unnecessary to remove pectin from the apple in order to make a more efficient therapeutic

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agent. Manville, Bradway and McMinis (5) showed that pectin acted as a detoxifying agent and concluded that this was due to the uronic acid content. The authors using chemically pure uronic acids, found that these acids had a detoxicating action on bacterial toxins (6). It is possible that this detoxifying action accounts for much of the curative action of the apple and pectin. Manville, Reithel and Yamada (7) have determined the sources of uronic acid in the apple. They found that pectin contributes 37.5 per cent of the uronic acid, and other factors 26.8 per cent, the presence of sugar giving an apparent value of 35.7 per cent. Recently a number of reports have appeared on the use of nickel pectinate and pectinates of other heavy metals in the treatment of dysentery and their bactericidal action *in vitro*. Block, Tarnowski and Green (8) treated a number of cases of bacillary dysentery with pectin and nickel pectinate. They found pure pectin to be ineffective while nickel pectinate was thought to be of therapeutic value. Arnold (9) studied the effect of the ingestion of nickel pectinate upon the growth of young rats to determine whether or not there was any toxic effect and found that 1256 mg. per kilogram of body weight did not influence the growth curve over an eight week period. Arnold (10) also tested the bactericidal action of nickel, cobalt, manganese, lead, zinc, copper, calcium and silver pectinates and stated that pectin possessed no bactericidal power while the metal pectinates were bactericidal in varying degrees according to the metallic ion. Silver pectinate was found to be highly bactericidal while the other pectinates acted to a lesser degree. These tests

were carried out at two hydrogen ion concentrations, namely at a pH 6.8 and 4.8. The concentrations of metals varied, the nickel being used in 0.3, 0.47 and 0.8 per cent and all of the others in 0.5 per cent. With the exception of silver pectinate, none of the other pectinates showed any exceptional bactericidal activity. In the case of nickel, when added in the form of a sulfate to pectin (0.05 per cent Ni) at a pH 4.8, the bactericidal action was greater than with nickel pectinate (0.8 Ni) at the same pH. In testing the activity of the pectinates with *B. typhosus*, *S. albus*, *S. aureus* and *Esch. coli*, Arnold showed that silver pectinate was the most bactericidal followed by copper and then nickel. However, the percentage of metallic ions used was high (0.5 per cent) and the pH of 4.8 rather low. At a pH 6.8 nickel pectinate allowed an increase in growth of *B. typhosus* and *S. aureus* and exerted an extremely weak action against *S. albus* and *Esch. coli*. In this particular tabulation the original count was not given thus making an evaluation difficult if not impossible.

In view of the fact that Arnold obtained better results with a lower concentration of nickel when the nickel was added to pectin than he did with the nickel pectinate and that throughout his experiments the concentrations of metals were high for the results obtained, it was decided to conduct the following experiments. Sulfate salts of copper, cobalt and nickel in various concentrations were added to nutrient broth and to nutrient broth containing two per cent apple powder (pectin content 8.5 per cent). These mixtures

TABLE I  
*Bactericidal action of copper in broth*

Organism Added	pH	Concentration of Metallic Ion in Per Cent	Time of Exposure in Hours and Bacterial Counts		
			0	6	24
<i>Esch. coli</i>	5.0	0.05	18,000,000*	0	0
" "	5.0	0.01	25,000,000	7,400,000	1,200,000
" "	6.0	0.05	14,000,000†	0	0
" "	6.0	0.01	19,000,000	6,000,000	2,400,000
<i>Staph. aureus</i>	5.0	0.05	25,000,000*	0	0
" "	5.0	0.01	12,800,000	4,000	0
" "	6.0	0.05	16,500,000†	0	0
" "	6.0	0.01	17,800,000	5,500	0

*Bactericidal action of copper in broth containing 2% apple powder*

<i>Esch. coli</i>	5.0	0.05	12,400,000‡	0	0
" "	5.0	0.01	16,000,000	3,100,000	920,000
" "	6.0	0.05	11,200,000§	0	0
" "	6.0	0.01	20,100,000	5,300,000	1,700,000
<i>Staph. aureus</i>	5.0	0.05	15,600,000‡	0	0
" "	5.0	0.01	10,300,000	5,800	0
" "	6.0	0.05	9,000,000§	0	0
" "	6.0	0.01	14,500,000	4,400	0

\*Cu 0.05 at pH 5.0—*E. coli* 0 hr. 18,000,000; 1 hr. 170,000; 2 hrs. 4,000; 3 hrs. 1400  
*S. aureus* 0 hr. 25,000,000; 1 hr. 300,000; 2 hrs. 1,200; 3 hrs. 0  
†Cu 0.05 at pH 6.0—*E. coli* 0 hr. 14,000,000; 1 hr. 1,440,000; 2 hrs. 20,100; 3 hrs. 6,500  
*S. aureus* 0 hr. 16,500,000; 1 hr. 510,000; 2 hrs. 6,000; 3 hrs. 101  
‡Cu 0.05 at pH 5.0—*E. coli* 0 hr. 12,400,000; 1 hr. 105,000; 2 hrs. 2,900; 3 hrs. 1,150  
*S. aureus* 0 hr. 15,600,000; 1 hr. 127,000; 2 hrs. 1,000; 3 hrs. 0  
§Cu 0.05 at pH 6.0—*E. coli* 0 hr. 11,200,000; 1 hr. 1,030,000; 2 hrs. 16,600; 3 hrs. 6,000  
*S. aureus* 0 hr. 9,000,000; 1 hr. 200,000; 2 hrs. 2,550; 3 hrs. 63

were then adjusted to various pH levels and tested for bactericidal action against *Esch. coli* and *S. aureus*.

### EXPERIMENTAL

Beef infusion broth was used as the basic medium and to this was added the metallic salt to be tested. Duplicate samples received in addition apple powder to a concentration of two per cent. Samples of each

were adjusted to pH 5.0 and 6.0, sterilized by autoclaving and the pH rechecked. All of the pH determinations were made with a glass electrode meter. *Staph. aureus* and *Esch. coli* grown for 18 to 24 hours in infusion broth were then added to the broth being tested, counts were taken immediately and at 6 and 24 hour intervals. The broth was kept at 37° C. throughout the test and all counts were made in triplicate and

TABLE II  
*Bactericidal action of nickel in broth*

Organism Added	pH	Concentration of Metallic Ion in Per Cent	Time of Exposure in Hours and Bacterial Counts		
			0	6	24
<i>Esch. coli</i>	5.0	0.05	41,000,000	110,000	19,500
" "	5.0	0.01	29,000,000	12,000,000	800,000
" "	6.0	0.05	22,000,000	890,000	105,000
" "	6.0	0.01	18,700,000	15,000,000	9,700,000
<i>Staph. aureus</i>	5.0	0.05	35,600,000	16,000	1,100
" "	5.0	0.01	19,000,000	1,100,000	74,000
" "	6.0	0.05	20,500,000	21,000	4,700
" "	6.0	0.01	16,100,000	3,900,000	880,000

*Bactericidal action of nickel in broth containing 2% apple powder*

<i>Esch. coli</i>	5.0	0.05	36,000,000	120,000	8,800
" "	5.0	0.01	24,500,000	10,000,000	1,000,000
" "	6.0	0.05	20,600,000	710,000	83,000
" "	6.0	0.01	21,000,000	13,600,000	10,200,000
<i>Staph. aureus</i>	5.0	0.05	30,000,000	17,100	1,050
" "	5.0	0.01	18,900,000	1,800,000	80,000
" "	6.0	0.05	16,000,000	14,000	2,600
" "	6.0	0.01	17,400,000	3,100,000	920,000

TABLE III  
*Bactericidal action of cobalt in broth*

Organism Added	pH	Concentration of Metallic Ion in Per Cent	Time of Exposure in Hours and Bacterial Counts		
			0	6	24
<i>Esch. coli</i>	5.0	0.05	9,100,000	1,100,000	0
" "	5.0	0.01	2,700,000	710,000	1,700
" "	6.0	0.05	5,000,000	900,000	0
" "	6.0	0.01	3,500,000	980,000	3,100
<i>Staph. aureus</i>	5.0	0.05	15,000,000	700	0
" "	5.0	0.01	3,800,000	20,000	97
" "	6.0	0.05	16,000,000	22,000	0
" "	6.0	0.01	2,500,000	40,000	162

*Bactericidal action of cobalt in broth containing 2% apple powder*

<i>Esch. coli</i>	5.0	0.05	12,700,000	300,000	0
" "	5.0	0.01	4,100,000	900,000	2,200
" "	6.0	0.05	5,500,000	600,000	0
" "	6.0	0.01	4,100,000	800,000	4,000
<i>Staph. aureus</i>	5.0	0.05	14,700,000	110,000	0
" "	5.0	0.01	3,500,000	15,500	9
" "	6.0	0.05	11,500,000	440,000	0
" "	6.0	0.01	4,100,000	51,000	200

averages reported. The tables are self-explanatory and give the results of the experiment.

### DISCUSSION

It will be noted from the tables that broth containing copper was the most bactericidal of the three metals tested and that it was more active against *S. aureus* than against *Esch. coli*. Cobalt was next in effectiveness and it also showed a more selective action against *S. aureus*. Nickel was definitely bactericidal but to the least degree and it, too, showed a selectivity for *S. aureus*. In all cases the action of the salts was greater at a pH 5.0 than at pH 6.0 which is of course in agreement with what is known of the bactericidal action of heavy metals. When mixtures of the salts were added to the broth their potency for *Esch. coli* was in the order of  $\text{Cu-Co} > \text{Co-Ni} > \text{Cu-Ni}$  and for *S. aureus* was  $\text{Cu-Co} > \text{Cu-Ni} > \text{Co-Ni}$ . It will be noted in Table IV and V that all viable organisms of *S. aureus* were destroyed within 24 hours in those tubes containing copper even though the concentration was as low as 5 mg. per cent.

In comparing the action of the metals in broth containing 2 per cent apple powder, parallel results were obtained. The addition of apple powder to the broth containing the metals, did not enhance or detract from the bactericidal action of the metallic ions.

The concentration of the metals added in these experiments was much less than those used by Arnold (10) and the bactericidal action was even greater. Arnold (10) found in one experiment (Arnold Table I) that 0.05 per cent nickel sulfate added to pectin was more bactericidal than the pectinate containing 0.8 per cent nickel. He did not, however, in like manner, test the other metals used as pectinates. It should be obvious from the above that in the treatment of intestinal disorders, the beneficial action of pectin may be enhanced more by the bactericidal action of metals when present as salts than when present in chemical combination as pectinates. Since the activity of the

metallic ions increases directly with the hydrogen-ion concentration, it would also be advisable to control this factor in their use.

A number of workers (11, 12, 13, 14) have found that the addition of such fruits as apple, banana, cranberry, etc., to basal diets tends to raise the hydrogen-ion concentration in the intestine. It would seem more logical then that if a bactericidal action is wanted in the intestinal tract, the addition of the metallic salt to the fruit would be more effective. From the standpoint of toxicity or cumulative effects, it is fortunate that a lower concentration of the metal is necessary than when it is present in the form of a pectinate.

The presence of the entire dehydrated apple in the intestine should have a decided advantage over the use of pectin alone. While it has been shown that the fruit in this form does not enhance the bactericidal effect of pectin and the metallic ions, neither does it detract from this effect. Other work done in this laboratory and elsewhere has shown that apple promotes a lower pH in the intestine; brings about an aciduric flora and acts as a precursor for butyric acid which is specifically more bactericidal than any of the other organic acids likely to be present in the intestine. The high potency of copper is extremely significant and, since it occurs in small amounts in apple (15), provides not only an added indication for the use of this foodstuff but offers in addition, a possible explanation of the effectiveness of apple diets in intestinal infections. Since the copper salts were effective in free form, sight should not be lost of the fact that sources of copper other than the apple may also be present in the intestine. There exists, also, the possibility that the added presence of small amounts of nickel or cobalt might maintain the effectiveness of copper even at lower concentrations. Furthermore, the natural acidity of the apple together with the acids developed from it in the intestine create an acidity that is within the

TABLE IV  
*Bactericidal action of mixtures of cobalt, copper and nickel in broth*

Organism Added	pH	Concentration of Metallic Ions in Per Cent			Time of Exposure in Hours and Bacterial Counts		
		Cu	Ni	Co	0	6	24
<i>Esch. coli</i>	5.0	0.005	0.005		10,400,000	9,200,000	2,900,000
" "	5.0	0.005		0.005	12,100,000	85,000	81
" "	5.0		0.005	0.005	17,000,000	1,100,000	6,000
" "	5.0	0.005	0.005	0.005	4,600,000	67,000	119
" "	6.0	0.005	0.005		9,100,000	11,000,000	5,600,000
" "	6.0	0.005		0.005	13,000,000	201,000	600
" "	6.0		0.005	0.005	5,000,000	2,800,000	15,000
" "	6.0	0.005	0.005	0.005	12,500,000	90,000	201
<i>Staph. aureus</i>	5.0	0.005	0.005		5,700,000	3,000	0
" "	5.0	0.005		0.005	7,300,000	1,000	0
" "	5.0		0.005	0.005	8,800,000	450,000	550
" "	5.0	0.005	0.005	0.005	5,400,000	500	0
" "	6.0	0.005	0.005		7,500,000	4,400	0
" "	6.0	0.005		0.005	10,800,000	3,600	0
" "	6.0		0.005	0.005	6,700,000	610,000	1,200
" "	6.0	0.005	0.005	0.005	6,200,000	1,100	0

TABLE V

*Bactericidal action of mixtures of cobalt, copper and nickel in broth containing two per cent apple powder*

Organism Added	pH	Concentration of Metallic Ions in Per Cent			Time of Exposure in Hours and Bacterial Counts		
		Cu	Ni	Co	0	6	24
Esch. coli	5.0	0.005	0.005		12,500,000	8,000,000	3,100,000
" "	5.0	0.005		0.005	10,000,000	67,000	90
" "	5.0		0.005	0.005	15,500,000	510,000	4,200
" "	5.9	0.005	0.005	0.005	9,000,000	93,000	210
" "	6.0	0.005	0.005		11,000,000	12,000,000	7,600,000
" "	6.0	0.005		0.005	10,000,000	120,000	200
" "	6.0		0.005	0.005	7,200,000	3,000,000	15,000
" "	6.0	0.005	0.005	0.005	9,100,000	58,000	174
Staph. aureus	5.0	0.005	0.005		7,500,000	2,800	0
" "	5.0	0.005		0.005	10,500,000	1,300	0
" "	5.0		0.005	0.005	6,700,000	400,000	620
" "	5.9	0.005	0.005	0.005	7,600,000	410	0
" "	6.0	0.005	0.005		6,000,000	5,000	0
" "	6.0		0.005	0.005	8,600,000	2,800	0
" "	6.0		0.005	0.005	7,000,000	510,000	1,400
" "	6.0	0.005	0.005	0.005	5,500,000	850	0

range of maximal activity of the bactericidal agents (16). The role of the staphylococcus in intestinal upsets cannot be inconsiderable when there is recalled the part this organism plays in the production of various toxins.

Another point in the use of apple powder is the presence of materials chiefly carbohydrate, of a caloric value. It is fortunate that the source of these calories is of such a nature that they will combat the development of an acidosis.

This work and the results of Arnold show that the addition to pectin of free metallic ions is more effective in vitro than when these metals are in combination with pectin. In vivo, it is highly probable that enzymatic activity does not allow the metal to be held in a bound state for very long. This possibility, if true, would explain the differences obtained in the in vitro tests.

### CONCLUSIONS

1. The addition of sulfate salts of copper, cobalt and nickel to nutrient broth in concentrations as low as 0.01 per cent of the metallic ion was definitely destructive of bacterial growth (*S. aureus* and *Esch. coli*).

2. The efficacy of the metallic ions is in the order named: copper, cobalt, nickel.

3. A pH of 5 was more effective than a pH of 6.

4. Copper in association with nickel or cobalt was equally effective at both pHs although its concentration was reduced to 5 mgs. per cent.

5. The presence in the culture media of dehydrated apple neither enhanced nor detracted from the effect but is advisable for the following reasons: it provides copper; it provides organic acids for proper pH adjustment; it provides materials from which other organic acids may be derived in the intestine which aid further in pH adjustment and act bactericidally themselves and it provides carbohydrate calories which are not only nutritive but which combat acidosis.

6. Metallic elements such as copper, cobalt and nickel are more effective in smaller concentration in the free form than when combined with pectin.

7. The copper naturally present in the apple (and perhaps cobalt and nickel) together with small amounts of these same minerals present from other sources in the intestine, offers a further explanation of the beneficial effect of apple diets in intestinal infections.

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# Relationship of the Diet to the Self-Regulatory Defense Mechanism

## III. Organic Acids and Pectin

By

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### INTRODUCTION

THE authors have shown in a preceding paper (1) that the feeding of a dehydrated apple supplement to rabbits increased the hydrogen-ion concentration of the intestinal contents. Also the intestinal flora was changed from one in which *Esch. coli* predominated to one in which the acidophilic type of organisms were dominant.

Bergeim, Hanszen and Arnold (2), using human volunteers, tested the influence of fresh fruit pre-meals (apples, bananas and oranges) upon the passage of living bacteria (*B. prodigiosus*) through the gastro-intestinal tract. With all three fruits, the test organism was found to be greatly reduced as compared with the controls. They further found that the *Esch. coli* were greatly reduced in the subjects fed fruit pre-

TABLE I

*Bacteriostatic action of acids showing greatest hydrogen-ion concentration at which there was growth of Esch. coli*

Acid	Growth (pH)	No Growth (pH)
Butyric	5.80	5.50
Lactic	5.00	4.85
Acetic	4.85	4.50
Malic	4.43	4.20
Maleic	4.60	4.35
Hydrochloric	4.60	4.40
Tartaric	4.85	4.60

meals. Determinations of the butyric acid present in the intestinal contents showed as high an amount as 578 cc. of 0.1 N. solution. They believed that this quantity of butyric acid assisted by acetic acid was definitely toxic to *Esch. coli*.

Haynes, Tompkins, Washburn and Winters (3), using pectin in vitro, found it to be bactericidal to *Esch. coli* at a pH of 5.5, but without effect at a pH of 6.0.

Since our rabbits fed a dehydrated apple supplement showed a decided diminution of *Esch. coli* and an increased hydrogen-ion concentration in the intestinal contents (1), it was decided to test the bactericidal and bacteriostatic properties of pectin and of the organic acids either present in the apple or that might be derived from it in the intestine. The dehydrated

apple used in our experiments contained 8.9 per cent pectin. If pectin or any of the organic acids are selectively bactericidal, it would help explain the change in flora of the gastro-intestinal tract in subjects fed apple supplements.

### EXPERIMENTAL

The test organism used for all of the bacteriostatic and bactericidal studies was an *Esch. coli* No. 260,

TABLE II

*Bacteriostatic action of mixture of acids*  
(Butyric 4 parts, Lactic 2 parts, Acetic 2 parts, Malic 2 parts)

Control pH 7.4	pH 6.9	pH 6.5	pH 6.1	pH 5.4	pH 5.0	pH 4.8
++++	-++++	++++	++++	++	+	-

kindly provided by Dr. Harry J. Sears of the Department of Bacteriology.

The following acids were tested for bacteriostatic properties: butyric, lactic, acetic, malic, maleic, tartaric and hydrochloric. The latter was tested because of its presence in the stomach and upper small intestine. The acids were added in various amounts to nutrient broth and the pH determined with a glass electrode pH meter. Each tube was then inoculated with *Esch. coli* from a 24 hour broth culture. Table I shows the pH at which there was growth and no growth for each acid. As shown, the acid having the

TABLE III

Butyric Acid pH	HCl Added to Final pH	Growth of <i>Esch. coli</i>
6.0	5.5	Growth
6.0	5.4	Growth
6.0	5.3	Growth
6.0	5.2	No growth

greatest bacteriostatic action is butyric. The order of bacteriostatic action is butyric>lactic>tartaric and acetic>hydrochloric>maleic>malic.

Since the organic acids would not be found alone in the intestinal contents, a mixture of butyric, four parts; lactic, 2 parts; acetic, 2 parts and malic, 2 parts, was added to broth and tested at different pH values. Table II shows the result of such a mixture.

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The mixture has about the same bacteriostatic action as lactic acid alone.

Butyric acid was further tested by adding it to broth until the pH was lowered to 6.0. Hydrochloric acid was then added until the desired pH was obtained and the bacteriostatic properties of this combination determined. Table III shows the results of such a mixture. In both the latter instances the presence of

TABLE IV

Figure indicates number of organisms per cc. of broth with pectin added to pH as indicated

Hours Exposure	Apple Pectin No. 1 pH 5.5	Apple Pectin No. 2 pH 5.5	Citrus Pectin pH 5.5	"Non-Acid Pectin" pH 5.5	Pectic Acid pH 5.5
0	76,000	59,000	81,000	95,000	79,000
24	416,000	1,950,000	810,000	9,220	5,640,000
48	11,060,000	30,000,000	12,300,000	3,776	31,700,000
Hours	pH 5.0	pH 5.0	pH 5.0	pH 5.0	pH 5.0
0	56,000	72,000	60,000	74,000	85,000
21	501,000	2,800,000	1,100,000	2,330	2,950,000
48	8,600,000	21,500,000	10,700,000	34	23,300,000

butyric acid improved the effect of lactic, acetic or hydrochloric acid above that obtained when these acids were used alone.

#### BACTERICIDAL AND BACTERIOSTATIC PROPERTIES OF PECTIN

The dehydrated apple used in previous work (1) contained 8.9 per cent of pectin. It was thought that this fraction should be tested for its bactericidal and bacteriostatic properties. Since pectin is quite acid in reaction, probably due in part to the pectic acid present, this latter fraction was tested also. The following materials were used: apple pectin No. 1 (Speas)\*, citrus pectin (B-3780)\*, citrus pectic acid (B-4136)\*, "non-acid pectin" (Grade 100)\*, and apple pectin No. 2 (produced in this laboratory by F. J. Reithel).

After our work with pectin had begun, Haynes, Tompkins, Washburn and Winters (3) reported that the addition of two per cent pectin to nutrient broth lowered the pH to 5.0-5.4 and that at these acidities there was a bactericidal effect. The organism used was an *Esch. coli*, the same type of organism as used in our experiments. Information concerning the method of preparation of the pectin used was not given and in view of the fact that in our preliminary experiments we found pectins to vary considerably, it was decided to add to our series a duplicate of the procedure of these authors\*.

To duplicate the procedure of Haynes et al, two per cent of the pectins sterilized at ten pounds pressure for thirty minutes were added to nutrient broth.

\*We wish to take this opportunity to express our very best appreciation to the Speas Manufacturing Company; to W. E. Baier of the California Fruit Growers Exchange and to the Sardik Laboratories, Inc., for supplying us with generous amounts of apple and citrus pectin, pectic acid and "non-acid pectin." Since this latter material was sent to us as non-acid pectin and was found to have a pH of 4.36 in a 2 per cent solution, we have taken the liberty of enclosing this term in quotation marks.

\*In a subsequent report it was stated that the pectin used was obtained from Sardik Laboratories. We were already in possession of a sample of this material which came to us under the label non-acid pectin and were subjecting it to the tests given in Table IV. Subsequent work by these investigators showed that the pectin used was in reality a nickel pectinate and not pectin at all (4).

Haynes found that two per cent pectin added to broth gave a pH of from 5.0 to 5.4. The method for determining the pH and the time allowed for an equilibrium to be established was not stated. When we tested the above solutions with a glass electrode pH meter and allowed sufficient time to elapse for the establishment of an equilibrium, the following reactions were obtained: apple pectin No. 1, pH 4.60; apple pectin No. 2, pH 4.61. Since these determinations were lower than those obtained by Haynes et al, these same pectins were made up in aqueous solution and added to broth until the desired hydrogen-ion concentration was reached. It was noted that when the pectins were added to broth the mixture did not immediately come to a pH equilibrium. Because of this, such mixtures were allowed to stand for two to three hours before a final pH determination was made. A known number of *Esch. coli* were added to the broth tubes and plate counts were made at 24 and 48 hours. Table IV shows the results of these experiments. Of the pectins tested, only the "non-acid pectin" gave results comparable to those of Haynes. The other pectins and pectic acid had no bactericidal or bacteriostatic action at a pH of 5.5 or 5.0. "Non-acid pectin" showed a bactericidal action, but it was not as great as that claimed for it by Haynes.

Although the hydrogen-ion concentration of our broth with two per cent pectin added differed greatly from that of Haynes, it was thought advisable to test the bactericidal power of these solutions. Table V gives the results of these tests. In the case of pectic acid, the two per cent addition gave a pH of 3.38. To give more comparable results with pectic acid, it was added to the broth until there was obtained the same hydrogen-ion concentration possessed by the apple

TABLE V

Twenty-four hour broth cultures of *Esch. coli* 0.1 cc. added to broth tubes and loop transfer made to nutrient broth at hours indicated. Growth recorded as +, no growth as —

Time of Exposure	2% Apple Pectin No. 1 pH 4.60	2% Apple Pectin No. 2 pH 4.61	2% Citrus Pectin pH 4.36	2% "Non-Acid Pectin" pH 4.36	2% Pectic Acid pH 3.38	Pectic Acid pH 4.60
15 min.	+	+	+	+	+	+
30 min.	+	+	+	+	+	+
45 min.	+	+	+	+	—	+
11 hrs.	+	+	+	+	+	+
12 hrs.	—	—	—	+	+	+
20 hrs.				+	+	+
24 hrs.				—	+	+
80 hrs.						+

pectin solutions. It will be noted from the results in Table V that at pHs of 4.6 to 4.36, the apple and citrus pectins were more bactericidal in 12 hours than "non-acid pectin." In Table IV, however, we find the reverse to be true; that is, that "non-acid pectin" is more bactericidal at a pH of 5.0. It would seem that the bactericidal property of "non-acid pectin" was due to something other than the hydrogen-ion concentra-

tion. Furthermore, it might be either that this same property is present in the other pectins in a smaller amount and that in order to show an effect the hydrogen-ion concentration had to be increased or that the results obtained in Table V were due entirely to an acid effect. Pectic acid at a pH of 4.6 was ineffective but at a pH of 3.38 it was quite active. This also is probably more of an acid effect than one due to the

TABLE VI

*Pectins (2%) in broth buffered with  $K_2HPO_4$  to pH indicated. Plate counts taken at once and after 48 hours exposure*

Original pH of 2% Pectin	Hours Exposure	Buffered to pH 4.85 Organisms Per cc.	Buffered to 5.0 Organisms Per cc.
Apple Pectin No. 1 pH 4.60	0 48	88,000 2,750,000	101,000 8,900,000
Apple Pectin No. 2 pH 4.61	0 48	57,000 3,100,000	60,000 10,500,000
Citrus Pectin pH 4.36	0 48	125,000 4,550,000	79,000 10,200,000
Non-acid Pectin pH 4.63	0 48	65,000 \$20,000	95,000 1,880,000
Pectic Acid pH 3.38	0 48	90,000 16,400,000	71,000 22,000,000

specific action of pectic acid itself. The loss of some of the effectiveness of "non-acid pectin" at a pH of 5.5 may be due to a decrease in the ionization of the active constituent since it has been concluded that the effectiveness of this material is not due entirely to the acidity it creates.

With the above in mind, tubes of broth containing two per cent pectins were buffered with  $K_2HPO_4$  to a more alkaline pH and tested as before. Table VI shows the results of these experiments. The plate counts made after 48 hours exposure show that alkaline buffering of pectin destroys or inhibits its bactericidal property though the pH was 4.85-5.0 in both instances. The presence of the alkaline buffer was least effective in the "non-acid pectin" solutions.

Since experimental animals fed the dehydrated apple supplement showed a decided decrease in *Esch. coli* (1), it was thought advisable to test solutions of

TABLE VII

*Bacteriostatic action of dehydrated apple added to broth to desired pH*

Hours Exposure	Number of Colonies at pH Indicated		
	4.6	5.0	5.2
0	71,000	63,000	81,000
48	2,760,000	4,900,000	15,500,000

the apple powder for bactericidal and bacteriostatic properties. The same procedure used for testing the pectins was tried with the apple powder. Table VII shows the results of the experiment with dehydrated apple. It will be noted that when the apple powder is added to broth to a pH of 4.6 no bacteriostatic action could be noted.

It may be that the cultural advantages of the presence of sugar are sufficient to nullify any detrimental effect of pectin or organic acids. In this particular instance, however, the pH was developed largely by malic acids. This acid has been shown to be ineffective above a pH of 4.2. Furthermore, pectin itself has not been shown to be bactericidal in vitro and the concentrations reached in this experiment did not nearly approach those used in the earlier experiments described herein.

Conditions produced in the test tube do not necessarily duplicate those present in the intestine. It did not require a large amount of dehydrated apple (pH 3.37-4.1) to bring the broth to a pH of 4.6. Such a condition while capable of existing in a test tube is hardly possible in the intestine because of the rapid removal by absorption of such materials as sugar. Furthermore, through absorption, insoluble residues are concentrated and from them are produced various organic acids as the result of bacterial and enzymic activity. These are some of the factors that make it very difficult, if not impossible, to simulate intestinal conditions in the test tube.

Nevertheless, it was advisable to test the effect of dehydrated apple after thorough alcoholic extraction. This removed the various sugars, fat, organic acids and the lower polymers of uronic acid. It left the pro-

TABLE VIII

*Bactericidal action of alcohol insoluble fraction of apple powder*

pH	0 Hour	24 Hours	48 Hours
6.15	5,040,000	11,680,000,000	32,140,000,000
5.0	2,040,000	67,200,000	807,000,000
4.5	1,600,000	4,710,000	6,500,000

tein, starch, hemicellulose, lignin and the higher uronic acid polymers (pectin). The residue of apple after slow extraction for five days was added to broth in quantities necessary to produce various degrees of acidity. Table VIII gives the results. Again the results were nil. Here, then, appears to be an instance of a material quite effective in the intestine in controlling bacterial types and growth but entirely without effect in the test tube. The factors thought to be potent in themselves have been shown not to be. Only one conclusion seems obvious and that is that such materials in the intestine give rise to substances which, in themselves, are inimical to certain organisms or which, in conjunction with other factors, as for example, certain minerals, become highly bactericidal.

## DISCUSSION

The bacteriostatic effect of butyric, lactic and acetic acids seems to be a specific property of these acids and not an acid effect. The fact that *Esch. coli* can grow at a pH of 4.43 produced by malic acid but are prevented from growing by butyric, lactic and acetic acids at higher pHs seems to prove this point. It is not known in what proportion the various organic acids exist in the intestine. However, the results shown in Tables II and III demonstrate further the striking bacteriostatic effect of butyric acid in its

ability to improve the inhibitory effect of lactic, acetic and hydrochloric acids.

The bacteriostatic effect of pectin seems to vary with its source. Apple pectin is just as effective at a pH of 4.6 as citrus pectin is at a pH of 4.36. The fact that pectic acid, a purer form of pectinous material than pectin, is ineffective at a pH of 4.6 (although the amount of pectic acid required to produce a pH of 4.6 is less than that of apple pectin) while apple pectin is, would seem to indicate that the effectiveness of the latter material was due to some attached substance. At a pH of 5, apple pectin had lost some of its effectiveness while "non-acid pectin" was quite potent although an amount smaller than that of apple pectin was required to produce a pH of 5.0. It would seem therefore that the effectiveness of "non-acid pectin" and apple pectin is largely a matter of pH, the former having its maximum activity at a pH of 5.0 and the latter at a pH of 4.6. When the various pectin preparations were made up in a two per cent solution, "non-acid pectin" produced the lowest pH (4.36). When these solutions were brought to a pH of 4.85 and 5.0 by the addition of  $K_2HPO_4$ , more had to be added to the "non-acid pectin" than to apple pectin. Nevertheless, in all instances, the bacteriostatic effect was lost. Adding enough phosphate buffer to produce a pH of 5.0 caused even a greater loss. This is a striking effect when it is recalled that "non-acid pectin" at a pH of 5.0 was very effective as a bacteriostatic agent. The explanation of this effect is not apparent unless it be connected in some way with the effect of the potassium or phosphate ions upon the active part of the pectin complex.

The fact that "non-acid pectin" is most effective at a pH of 5.0 and apple pectin at a pH of 4.6 indicates the possibility that the active factor associated with pectin is not the same in both instances. Furthermore, the effectiveness of "non-acid pectin" (nickel pectinate) at a pH of 4.36 was not as great as that of apple pectin at a pH of 4.6. The effectiveness of apple pectin at various hydrogen-ion concentrations deserves more study.

## SUMMARY AND CONCLUSIONS

1. Of the organic acids present in the intestinal contents of animals fed fruit supplements, butyric acid has the greatest bacteriostatic effect.
2. The bacteriostatic action of butyric acid is not entirely dependent upon the hydrogen-ion concentration.
3. Bactericidal action of the pectins vary with their composition, and the pH of the medium.
4. "Non-acid pectin" was found to be bactericidal at a pH of 5.0-5.5 but the other pectins tested were not.
5. As the pH was lowered to 4.6 apple and citrus pectin became more bactericidal than the "non-acid pectin."
6. Pectic acid was less inhibitory than pectin at the same pH.
7. Solutions of the various pectins brought to a pH of 4.85 and 5.0 by  $K_2HPO_4$  lost their bacteriostatic effect.
8. Dehydrated apple powder has no bactericidal or bacteriostatic action at a pH as low as 4.6. The removal of alcohol soluble materials from the apple did not improve the anti-bacterial effect in vitro.
9. The possibility is discussed that the bactericidal effect of such food materials as the apple in the intestine is not so much due to substances contained in them as to factors derived from them by enzymic action. There remains in addition the possibility that certain inorganic elements present may be effective and that pectin under certain conditions such as an optimum pH may exert an inhibitory or destructive effect upon bacterial growth.

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## Aneurysm of the Abdominal Aorta\*

By

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**A**NEURYSM of the abdominal aorta is a relatively rare condition. It was first described by Vesalius (1) in 1557. A survey of the current literature on this subject reveals a number of single case reports and a few reviews. The incidence of this condition in hospital records is extremely low, ranging about 0.035 per cent. The necropsy incidence however is much higher, ranging about 0.173 per cent. The abdominal constitute 11.8 per cent of all aneurysms. The total number of reported cases is less than 500. Nixon (2) in 1911 collected 233 cases, and Kampmeier (3) in 1936 brought the number up to 381.

The majority of cases occur in the negro race, because of their high incidence of syphilis. In 335 cases there were 292 males and 43 females.

Three types of aneurysms are recognized; the saccular, fusiform and dissecting. In 34 of 38 cases of abdominal aneurysm, Lucke and Rea (4) found that 30 were saccular, 3 fusiform and 1 of the dissecting types. Aneurysmal sacs vary in size, may be either small or large. The majority, however, are quite large when recognized. An unusually large sized tumor mass may at times be visible on inspection of the abdomen. The ability to disclose the aneurysmal mass varies according to its size and position. When the

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Fig. 1, Case 1. A 24 hour gastro-intestinal roentgenogram demonstrating an abdominal aneurysm situated mesially, adjacent the 2nd and 3rd lumbar vertebra at arrows A. Note the calcification of the abdominal aorta at arrow B. The psoas muscle is clearly visible, can be seen through the sac.

aneurysm arises from the anterior wall of the aorta, the tumor mass is detected by its expansile, pulsating characteristics, while those arising from the posterior wall present greater difficulty in palpating, except when they are very large in size. In our two cases, one was very small and not palpable, the other was very large and palpable. The mass is frequently expansile, a sign which is more or less pathognomonic of this condition. According to Osler (5), the presence of an expansile tumor mass in the abdomen justifies a diagnosis of an abdominal aneurysm. However, it must be emphasized that all aneurysms do not pulsate, and one must rule out the possibility of transmitted pulsations.

Aneurysms may occur in any portion of the abdominal aorta. They are most commonly observed in the upper segment of the aorta near the celiac axis. The site of the aneurysmal mass is usually limited by the vertebra and liver, so that nearly all abdominal aneurysms are situated on the left side.

Calcification of the abdominal aorta and calcification of the aneurysm may be observed in some instances. The calcified plaques may outline the aneurysmal sac clearly. In Kampmeier's 68 cases only 3 revealed a calcification of the sac of the aneurysm. In 80 cases of intra-abdominal aneurysms of all types, Mills and Horton (6) found 5 instances with calcified deposits in the aneurysmal sac.

A highly important and not uncommon roentgen finding in this condition is the erosion of the vertebra by pressure of the aneurysmal sac upon the spine. The

number of vertebra involved vary, but two or more bodies are commonly affected. The region most often involved lies between the 12th dorsal and 3rd lumbar vertebra. The 12th dorsal and 1st lumbar vertebra are the two most often involved. An interesting phenomenon, characteristic of this condition is the lack of involvement of the intervertebral disc. The disc is rarely affected in the erosive process until very late in the course of the disease. The absence of disc involvement produces a characteristic pressure deformity of the bodies of the vertebra in the form of a saucer-shaped mid-portion or scalloping. The superior and inferior margins of the body adjacent to the discs are usually intact. The erosion is smooth and clear-cut and varies from a slight pressure defect on the anterior surface to an extensive deformity involving as much as one-half of the body of the vertebra. Ordinarily the erosive process continues until a deep excavation is made producing a crescent shaped deformity. It has been pointed out that the preservation of the disc is attributed to the resiliency of the cartilage. The incidence of spinal involvement varies, but it is said to be quite large. In 24 of Kampmeier's 68 cases in which studies of the spine were made, 18 or 75 per cent of these yielded evidence of erosion of the vertebra. Vertebral erosion may be so marked as to cause compression of the spinal cord. Gregory (8) emphasized that compression of the spinal cord as a complication of abdominal aneurysm has received but too little attention. Weingrow and Bray (9) report a case of abdominal aneurysm in which lipiodol injected

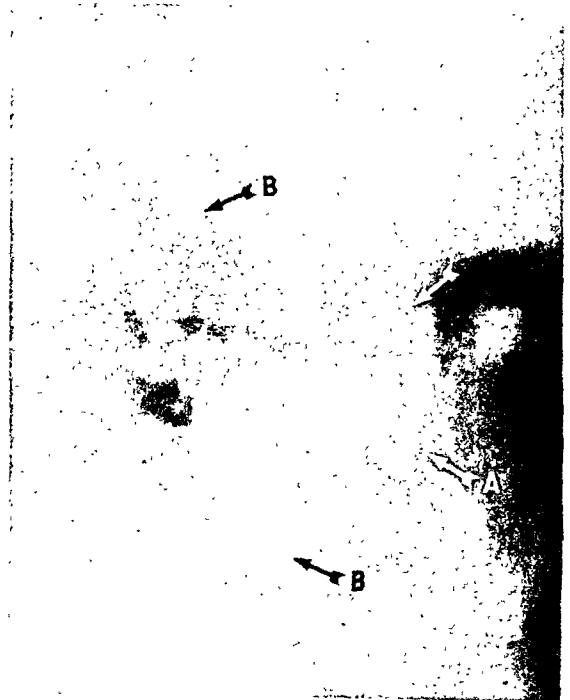


Fig. 2, Case 1. Lateral view of abdomen, the aneurysmal sac is shown at arrows A. Calcification of the abdominal aorta is demonstrated at arrows B (retouched). The lumbar vertebra do not show evidence of pressure erosion.



Fig. 3, Case 2. Demonstrates a large fusiform abdominal aneurysm in a preliminary roentgenogram made in the supine position. The sac extends from the 12th dorsal vertebra to the 4th lumbar vertebra (retouched). Note the psoas muscle is clearly visible.

into the spinal canal revealed an obstruction due to pressure.

Pressure deformities and bone erosion of the lower left ribs and also separation of the ribs have been noted in some cases of abdominal aneurysm. Farmer (7) directs attention to signs of rarefaction of the lower left ribs and also the transverse processes of the left side of the lumbar vertebra as the result of pressure.

Abdominal aneurysm frequently terminate by retroperitoneal and intraperitoneal rupture. It may, however, rupture into the abdominal viscus. Rarely it may rupture through the diaphragm into the pleural cavity. Such instances were reported by McClure (10), and by Croly and Graves (11). A ruptured aneurysm may in rare instances produce an intestinal obstruction. The necropsy incidence of rupture of abdominal aneurysms vary. The following table presents the incidence in a large series of autopsy cases.

	Autopsy Cases	Rupture	Rupture Into Duodenum	Rupture Into Abdominal Viscus
Neely (12)	1,385	5	1	
Kampmeier (3)	381		4	10
Nixon (2)	233	149		3
Marlow and Doubler (13)	214			5

Owing to the close proximity of the duodenum to abdominal aneurysms, rupture into this portion of the intestine occur with greater frequency than in other parts of the gastro-intestinal tract.

Clinically the condition manifests itself variously. It may not produce any clinical manifestations whatsoever, but on the other hand, may cause considerable abdominal distress, depending upon the amount of pressure on the neighboring organs. It is interesting to note that of the 80 cases of intra-abdominal aneurysms reported by Mills and Horton, gastro-intestinal symptoms were present in only 7 instances or 8.08 per cent.

#### CASE REPORTS

During a period of five years two cases of abdominal aneurysm were encountered at the Sinai Hospital. A brief report of these two cases is presented.

Case 1, S. P., male, aged 63, complained of pains in both arms and legs with some difficulty in walking. He also complained of genito-urinary symptoms, such as dribbling and incontinence. There was evidence of a chronic myocarditis and cardiac insufficiency. There were no clinical manifestations that indicated the presence of an abdominal aneurysm. There was a prostatic benign hypertrophy. Studies of the kidney including pyelographic examination yielded evidence of a hypernephroma of the right kidney. The Wassermann test was negative. A routine roentgen examination of the gastro-intestinal tract showed a small 5½ hour gastric residue, otherwise nothing abnormal was found. The gastro-intestinal films showed a shadow in the left upper quadrant situated mesially, close to the spinal column. A lateral view showed the mass connected with a calcified abdominal aorta. The aneurysmal sac also revealed evidence of calcification. The



Fig. 4, Case 2. Roentgenogram of the stomach illustrating a large pressure defect, compressing the pyloric portion of the stomach. Note the mucosa rugae are not effaced. The stomach is displaced toward the left side.

small aneurysmal mass was not palpated. A roentgen diagnosis of abdominal aneurysm was made.

Case 2, R. G., female, aged 74, referred to the Sinai Hospital by Dr. A. L. Hornstein. She presented marked hypertensive cardiovascular disease with cardiac insufficiency and hypertrophy. Her blood pressure was 190/136. Wassermann test was negative. Examination of the abdomen revealed a large mass, palpated on the left side mesially. This mass was not definitely expansile. A gastro-intestinal roentgen study revealed a large filling defect in the pyloric portion of the stomach. The rugae in the defective area was not entirely effaced. The defect was definitely due to pressure from an extrinsic mass. There was also a duodenal diverticulum. A roentgen diagnosis of an extrinsic mass causing pressure upon the stomach was made. A preoperative diagnosis of a possible abdominal aneurysm was made by Dr. T. S. Cullen.

### DIAGNOSIS

The diagnosis of abdominal aorta aneurysm is frequently attended with great difficulty. It should be considered in all retroperitoneal tumors, especially those arising on the left side and mesially. The condition may elude discovery in spite of a thorough investigation. A preliminary roentgenogram of the abdomen made in the supine position will often reveal an aneurysmal tumor mass adjacent to the spinal column. At times calcareous plaques in the wall of the sac will clearly outline the aneurysm. Fluoroscopic examination may disclose a fixed mass when palpable, which does not move with respiration. The mass is adherent mesially and is not connected to any of the radiable organs. The mass may be seen to pulsate at times. The psoas muscle is not generally obliterated in the uncomplicated case, but in cases of retroperitoneal hemorrhage or rupture, the outline of the psoas muscle may be obscured. The left kidney may be displaced peripherally to the left. In cases of rupture retroperitoneally, the kidney outline may be obscured. If rupture has occurred, a diffuse density may be seen in the retroperitoneal space. If the aneurysm is located high up under the left diaphragm it may be brought out in relief by the air bubble in the stomach or air in the colon. A lateral view of the spine will often disclose the typical scalloped appearance of the vertebra.

A gastro-intestinal examination will frequently reveal signs of extrinsic pressure in the stomach. The stomach may be displaced toward the left side and

anteriorly. The left colon may also show evidence of pressure and downward displacement when the tumor sac is very large. The pressure defect and displacement of the stomach depends upon the position and size of the aneurysm. When the aneurysm is situated in the upper segment of the abdominal aorta, pressure changes in the stomach are more apt to be observed, while those that occur in the lower portion of the aorta do not as a rule produce gastric pressure. A gastro-intestinal fluoroscopic study may occasionally reveal abnormal transmitted gastric pulsations, due to the pulsating aneurysm against the wall of the stomach. There is often pressure on the third portion of the duodenum. Washburn and Wilbur (14) point out that obstruction of the 3rd portion of the duodenum is relatively common. The aneurysmal mass does not as a rule move with respiration and when situated close to the diaphragm, may be seen to separate from it.

A roentgenogram of the chest may disclose an elevation of the left diaphragm and heart shadows as a result of pressure from below. In the case of a spurious aneurysm Kjellberg (15) points out that a rounded hernia-like protrusion of the posterior portion of the diaphragm may simulate a neoplasm. Various special roentgenographic procedures have been recommended in order to better demonstrate the aneurysmal mass. Spangenberg, Munist and Letjman (16) advocate the use of aortography by the injection of an opaque medium into the aorta in order to outline the sac. Pneumoperitoneum has also been used by some as an aid in outlining the aneurysm. Air insufflated into the colon may in some instances bring out in relief an aneurysmal sac.

### SUMMARY

Aneurysm of the abdominal aorta is a relatively rare condition. In a period of five years only two cases were observed. The condition may be diagnosed roentgenologically in a large percentage of cases. The roentgen criteria of a tumorous sac formation, calcium deposits in the sac, retroperitoneal mesial position of the tumor, a mass demonstrated to be outside of the gastro-intestinal organs, which cause pressure and displacement of the stomach; pressure erosive defects of the vertebra and an expansile tumor mass, are signs of aneurysm of the abdominal aorta. Two cases are reported with a survey of the literature.

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# The Emptying Time of the Normal Human Stomach as Influenced by Acid and Alkali With a Review of the Literature\*†

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IT is commonly believed as established that alkalies cause the stomach to empty faster and acids cause it to empty slower. When one, however, reviews the literature pertaining to the subject, from the viewpoint of methods used, the evidence submitted, and the discrepancies reported, one finds that the matter is not as well established as it should be in view of the common use of alkalies and acids in therapy. In order to support the truth of the preceding statements, the literature will be briefly reviewed; this is necessary also in order to gain a proper perspective of this problem.

## REVIEW OF THE LITERATURE

Hirsch is usually regarded as the first worker to investigate the action of acids and alkalies on the stomach. Reports may be found in the literature, however, bearing on phases of this problem which antedate Hirsch's work by nearly a quarter of a century. Kussmaul (1) in 1869 reported that gastric peristalsis was greatly increased when the stomach was insufflated with carbon dioxide; this substance is, of course, a very weak acid. Jaworski (2) in 1884, also reported that gastric emptying was hastened by carbon dioxide.

Alvarez (3) has emphasized the fact that considerable interest had been shown in the action of acids and alkalies on the stomach and on the pylorus before the work of Hirsch appeared. Ewald and Boas (4) in 1868, stated that their experiments suggested that the presence of acid controlled the pylorus. Von Pfungen and Ullman (5) in 1887, observed that in a patient with a gastric fistula the tone of the pylorus was affected by acids and alkalies. They found that 0.3 per cent of hydrochloric acid produced no particular change in the activity of the stomach, but alkali increased the number and depths of gastric peristaltic waves. Oppenheimer (6) in 1889, was well acquainted with the prevalent ideas concerning the role acid was thought to play in controlling pyloric opening, but he, with prophetic insight, suggested that the opening of the pylorus was probably a function of the bowel rather than the stomach. Ewald (7), in 1891, however, wrote that most authors were inclined to the view that gastric emptying depended normally upon the degree of acidity present.

Hirsch investigated the action of acids and alkalies on the stomach in dogs with duodenal fistulae; making his first report in 1892 (8) he concluded that neutral, alkaline or acid solutions had no effect on the pylorus.

A year later (9), however, he came to the conclusion, after working with certain inorganic and organic acids (phosphoric, tartaric, sulphuric, butyric, citric and lactic acids) that the action of acid on the intestinal mucosa influenced the emptying of the stomach.

Serdjukov (10), in 1898, made a careful study of the action of acids and alkalies on the pylorus and on gastric emptying. Using dogs with chronic gastric and duodenal fistulae, he observed that neutral water, 0.25 per cent and 0.5 per cent of sodium bicarbonate, hydrochloric acid of like strength, and the normal gastric juice of dogs left the stomach about with equal rapidity, with the possible exception of the alkali which he felt probably left the stomach a little faster. When solutions containing acid, however, were placed in the duodenum, gastric emptying was retarded.

Moritz (11), in 1901, using man as a subject and using the stomach tube method, confirmed the fact that strong acids slowed the emptying time of the stomach. Meyer (12), in 1903, studied the rate of gastric emptying in men with subacid and hyperacid stomachs. He used two types of test meals, one which consisted principally of carbohydrates and another of proteins. The stomachs were pumped out at the end of an hour and the amount of dry substance remaining was determined; no significant difference was observed. Lintvareff (13), in 1903, working with dogs with gastric and duodenal fistulae, came to the conclusion that the acidity or the alkalinity of the gastric contents had no effect upon the passage into the duodenum of the initial portion of the meal.

Carnot and Chassevant (14), in 1905, studying the effects of acidity and of osmotic pressure at the same time on gastric emptying found that strong acids leave the stomach slowly, but if the osmotic pressure reached a certain point they left the stomach rapidly. Hedblom and Cannon (15), in 1909, reported that acid solution up to 0.25 per cent hastened gastric motility and that it was only when 1 per cent of acid was used that the motility was lessened. Tabora (16), in 1911, using man as a subject and using the X-ray, found that if hydrochloric acid were added to bismuth and the latter ingested, gastric emptying would be markedly retarded. He failed to mention what strength acid he used. Cowie and Lyon (17), in the same year, working with infants, found that the addition of either acid or alkali to the meal retarded the emptying of the stomach. Binet and Lebon (18), in 1912, working with patients who suffered from various gastric maladies, reported that the ingestion of 5 grams of sodium bicarbonate stimulated gastric mo-

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tility. A dose of two and one-half grams had no effect on gastric emptying and 10 grams caused some inhibition. They concluded that the carbon dioxide liberated by the hydrochloric acid in the stomach caused the increased gastric motility.

Lenk and Eisler (19), in 1913, reported that strong acid solutions delayed gastric emptying. They also reported that alkalies hastened gastric emptying. Their experiments, however, could hardly be considered physiologic since they gave 2 "coffee-spoonfuls" of magnesium oxide to cats. As Alvarez (3) has suggested, their experiments belong more to the field of pharmacology than physiology. Ladd (20), in 1914, working with infants, found that if sodium bicarbonate were added to the food, gastric emptying was hastened.

In 1915, Spencer, Meyer, Rehfuess and Hawk (21) determined gastric emptying time in adults by means of a stomach tube. They reported that 5 per cent sodium bicarbonate remained in the stomach until the alkalinity was reduced—by secretion of hydrochloric acid—to a point where it was no longer irritating to the duodenum. One per cent of sodium bicarbonate, however, hastened gastric emptying; they felt that this concentration of the alkali either increased gastric motility or opened the pylorus.

Neilson and Lipsitz (22), in 1915, studied the gastric emptying time in man also using the stomach tube method. Five hundred cc. of water was used as a control. The effect of hydrochloric acid (1 per cent) was studied and also the effect of sodium bicarbonate (5 grams in the 500 cc. of water). They reported that normal acidity caused more rapid gastric emptying than artificially produced hyperacidity and that the artificially produced alkalinity caused the stomach to empty slightly less rapidly than water under normal conditions, but the sodium bicarbonate did not retard gastric emptying as much as did the acid. Egan (23), in the same year, also working with man as a subject and using liquids given by the stomach tube, reported indeterminate results with acids on the gastric emptying time. Theile (24), in 1917, also used the stomach tube on humans. He used milk, however, in his studies and came to the same conclusion as did Egan, that acid had but little effect, if any, on gastric emptying. He did find, however, that moderate alkalization hastened gastric emptying.

Morse (25), in 1916, working with pithed splanchnicotomized dogs, found that neutral water left the stomach faster than that which had been acidified. In fact, he reported that the stronger the acid, the greater the gastric delay. McClure, Reynolds and Schwartz (26), in 1920, investigated the action on the human pylorus of acids and alkalies instilled by a tube on both the antral and the duodenal sides of the pylorus. On the antral side these substances had no effect on the sphincter, but on the duodenal side they observed duodenal antiperistalsis accompanied either by pylorospasm or inhibition of antral peristalsis in two instances. Carnot and Koskowski (27), in 1922, using both dogs and man, reported that carbonic acid hastened gastric emptying. In man they found that either installation of the carbonic acid in the stomach by means of an Einhorn tube or by subcutaneous injection, notably augmented gastric motility. Baird, Campbell and Hern (28), in 1924, using man as a subject and using both stomach and duodenal tubes,

reported that in order for acid solutions to leave the stomach rapidly, partial neutralization was necessary.

Ortner (29), in 1927, working with dogs and using a Dastre cannula, which he placed a few centimeters below the pylorus, found that alkaline fluid passed through more readily than did acidified fluid. Hydrochloric acid above the strength of 0.3 per cent inhibited relaxation of the sphincter. Marks (30), a year later, working with dogs with duodenal fistulae, found that with the increase in the acidity of the meal, there was a concomitant delay in gastric emptying. Degener (31), in the same year, using methods very similar to those of Spencer, Meyer, Rehfuess and Hawk (21) confirmed their previous work.

Serby and Dooley (32), in 1930, placing the isolated frog's stomach in an oncometer, studied the effects of acidity and basicity. They reported that hydrochloric acid (0.4 to 0.8 per cent) favored peristalsis and caused a freer outflow from the stomach; alkali (sodium hydroxide 0.05 to 0.07 per cent) was found to decrease the number of antiperistaltic waves and to reduce the output.

Elman and Rowlette (33), in 1931, studying the gastric emptying time in dogs which had had a pyloroplasty, found that postoperatively a solution of a 0.5 per cent hydrochloric acid was expelled more rapidly than it was before the pyloroplasty was performed. Stewart and Boldyreff (34), in 1932, working with dogs with gastric fistulae, found that the stomach evacuated a solution containing 0.5 per cent of hydrochloric acid about at one-third the speed of that of the same amount of water.

Thomas, Crider and Mogan (35), in 1934, working with dogs with gastric and duodenal fistulae, reported that hydrochloric acid injected into the stomach near the pyloric sphincter had no significant effect on the tonus of this structure. When hydrochloric acid was placed in the duodenum, however, there was a temporary increase in the tonus of the pyloric sphincter which was followed by a moderate relaxation and inhibition of the rhythmic contractions. These authors pointed out, however, that acid of sufficient strength to cause an increase of pyloric tone probably does not reach the duodenum under normal conditions.

Shay and Gershon-Cohen (36), in the same year, studied the effects of hydrochloric acid (0.09 to 0.53 per cent) and sodium bicarbonate (1 to 5 per cent) on gastric motor function and on the pylorus on man. Three types of patients were selected: a group who gave a normal gastric secretory response to the Ewald test meal; secondly, a group whom they classified as hyperchlorhydric; and thirdly, a group classified as achlorhydric. They reported that the effects of acids and alkalies on gastric emptying depended upon the gastric secretory response of the subject. Weak acid (0.09 to 0.23 per cent) added to the test meal had no effect on the gastric emptying time on patients who responded normally to the Ewald meal or to the group of hyperchlorhydric patients. It caused a marked delay (50 to 150 per cent), however, in the achlorhydric patients. Strong acid (0.24 to 0.53 per cent) caused a marked delay in all three groups of patients.

When 1 per cent of sodium bicarbonate was used, the gastric emptying time was decreased in the normal and in the hyperchlorhydric group, but no effect was observed on the achlorhydric group. When a 5 per cent



sodium bicarbonate solution was used, the effect on the gastric emptying of the normal group was indeterminate; in the hyperchlorhydric group a decrease was noted in 6 out of 7 patients; in the achlorhydric group, however, the 5 per cent solution of sodium bicarbonate caused a definite retardation of gastric motility in all the patients.

These authors insist that in order to interpret properly the action of acids or alkalies on gastric emptying time, the gastric secretory response of the subject must be known. They further believe that some of the conflicting results reported in the literature are due to taking no cognizance of this fact.

From this review of the literature, it may be seen that the effect of acids and alkalies on the stomach and the pylorus has engaged the attention of both professional physiologists and clinicians for many years. The literature shows that most workers agree that if strong acid be added to the gastric contents, gastric motility is inhibited, whereas weak acid has an inde-

TABLE I

*Effect of hydrochloric acid on gastric emptying time*

Subject Number	Normal Hrs.	After HCl	Per Cent Change	"p"*
1	1.66	2.12	+27.7	
2	2.33	2.87	+23.2	
3	1.94	2.25	+16.0	
4	2.33	2.67	+14.6	
5	2.25	2.50	+11.1	
6	2.08	2.17	+ 4.3	
7	1.50	1.50	0.0	
8	2.17	2.17	0.0	
9	2.08	1.75	-15.9	
Average	2.04	2.22	+ 9.0	>0.3

\*"p" refers to chance occurrence, calculated according to Fisher (35).  
A "p" of 0.05 is regarded significant (i.e. 5 chances in 100 or one in 20, that it occurred by chance).

terminate effect. Most workers too agree that average doses of sodium bicarbonate generally hasten stomach emptying, but there is considerable evidence that large doses of alkali may inhibit gastric motility.

It is indeed singular, however, that of all the investigators who have worked on this problem there is apparently no record of any one having made simple quantitative studies of the action of the commonly used acids and alkalies on the emptying time of the human stomach in response to a physiologic test meal. Because of this, the authors felt that such a study should be made and that doses of acid and alkali which correspond to the ordinary therapeutic doses used by clinicians should be used.

#### METHODS

Adult male medical students volunteered as subjects for this work. The presence of hydrochloric acid in the gastric secretions of each was established by previous determinations. The subjects were given a standard radio-opaque meal, the preparation of which has been described in detail elsewhere (37). It consisted essentially of 15 grams of Quaker Farina, cooked to a constant volume with water, with 50

grams of barium sulphate added, after cooling, to produce radio-opacity.

The subjects were given the test meal at about 8:30 a.m., having fasted since the previous evening meal. They were encouraged to rest, mentally and physically, during the test period. The subjects were examined fluoroscopically at appropriate intervals, and the time

TABLE II

*Effect of sodium bicarbonate on gastric emptying time*

Subject Number	Normal Hrs.	After NaHCO <sub>3</sub> Hrs.	Per Cent Change	"p"*
1	2.17	1.42	-34.6	
2	2.08	1.50	-27.9	
3	2.17	1.58	-27.2	
4	2.17	1.75	-19.3	
5	2.06	1.67	-18.9	
6	2.30	2.00	-13.0	
7	2.00	1.75	-12.5	
8	1.50	1.42	- 5.3	
9	2.08	2.00	- 3.8	
10	1.92	1.92	0.0	
Average	2.05	1.70	-16.3	>0.01

\*See note on foot of Table I.

when the last of the opaque material left the stomach was noted to the nearest ten minutes. After a good average normal had been established for each individual the experimental conditions were instituted.

Hydrochloric acid was studied as follows: The standard test meal was consumed in the usual way, and immediately after it was finished the subject drank, through a glass tube, one hundred cc. of a solution containing two cc. of diluted hydrochloric acid, the usual therapeutic dose. At least three or four such determinations were made upon each individual upon different days, and an average figure established.

Sodium bicarbonate was then studied. One hundred cc. of 5 per cent solution of this alkali was adminis-

TABLE III

*Effect of di-sodium phosphate on gastric emptying time*

Subject Number	Normal Hrs.	After Na <sub>2</sub> HPO <sub>4</sub>	Per Cent Change
1	2.17	1.53	-24.9
2	2.50	2.00	-20.0
3	1.87	1.75	- 6.4
Average	2.18	1.79	-17.1

tered by mouth immediately after the subject finished the meal. This corresponds to the usual clinical dose and mode of administration. The emptying time of the stomach was then determined in the same manner as was used when the effect of hydrochloric acid was studied. Another alkali, di-sodium phosphate, was studied in a few subjects. The mode of administration

was the same as with the other substances and the dose was 4 grams, the usual therapeutic dose, dissolved in 100 cc. of water.

Previous work has shown that the ingestion of 100 cc. of tap water immediately following the test meal has no appreciable effect on the emptying time of the stomach.

## RESULTS

Table I outlines the results obtained with the hydrochloric acid. In five of the nine subjects there is a distinct delay. Three subjects were substantially unaffected, while the emptying time of the stomach of one individual apparently was hastened by the acid. The table shows that there was a 9 per cent delay in the gastric emptying time. When the data were statistically analyzed, however, the difference was found not to be significant. The results must then be interpreted to mean that with the amounts of acid used the effect was indeterminate.

Table II shows the results obtained when 100 cc. of 5 per cent sodium bicarbonate was administered. Seven of the ten subjects show a rather marked reduction in the gastric emptying time, while the remaining three are scarcely affected. Statistically analyzed, the results appear highly significant, the probability of the results occurring by chance is less than one in one hundred.

Table III shows the effects of di-sodium phosphate on the gastric emptying time. This substance was used so as to determine whether the hastening of gastric evacuation after the administration of sodium bicarbonate was due to an alkalinizing action or to the effect of the liberation of carbon dioxide. Since this work was largely corroborative in nature, fewer subjects were used. It will be seen that gastric evacuation was distinctly hastened by the di-sodium phosphate.

## DISCUSSION

The normal emptying time of the stomach for the test meal used in this work appears to be fairly well established. A previous report (37) on the emptying time in nine normal subjects using this meal showed an average of 2.08 hours. Since this report, many more subjects have been used, so that the total is now 37. The average emptying time for the 37 subjects is practically the same as it was for the 9 subjects reported. There are rather wide individual variations; the shortest time of any individual, however, remains remarkably constant from day to day. This individual variability undoubtedly accounts for the fact that the normal for the three subjects used in the work with the di-sodium phosphate is somewhat longer than that of the larger series used in each of the other sets of experiments.

The results show considerable individual variation in the response to each of the three agents studied; similar, although less marked, variations have been noted by the authors when the effect of other substances on the gastric emptying time was investigated (39, 40, 41). It is difficult to explain these wide individual variations produced by acids and alkalies. The fact that these substances do affect individuals differently may account for the conflicting reports in the literature concerning the action of these substances on gastric emptying. In view of the work of Shay and Gershon-Cohen (36), which has been mentioned previ-

ously, it may be that the level of acid secretory function of the stomach at the particular time of any test might have some bearing on the effect of added acid or alkali. Bloomfield and Keefer (42), however, could not find any relationship between the motility of the stomach and the acidity of the gastric juice. It was thought best not to attempt to determine the acidity of the gastric juice before the meal was ingested since the introduction of a tube in subjects unaccustomed to this procedure might destroy the previously entirely physiologic method used. We did know, however, that each subject used in this work had been found to have hydrochloric acid in his gastric juice.

The results here agree in general with those obtained by the majority of workers that moderate alkalization of gastric contents hasten gastric emptying. The insignificant delay caused by the administration of the acid is perhaps best explained by the fact that the dosage of acid employed (average therapeutic dose) produced a low acidity compared to some of the amount used by other investigators. The concentration of the acid ingested was 0.70 per cent; after dilution by the meal it was only 0.27 per cent. Considering the fact that a considerable amount of the acid would be combined with the meal, not much change in the pH would be expected. Since this paper is concerned with the effect of therapeutic doses of acid and alkali, the administration of larger doses of acid which might have produced a significant delay in gastric emptying was not attempted.

The exact mechanism responsible for the results reported in this paper is by no means clear. Three possible mechanisms suggest themselves: an effect on the pylorus; a stimulation of motor activity associated with stimulation of the secretion by the alkali; and a direct effect on the gastric musculature. None are without their objections. These mechanisms will now be considered.

In view of the divergence of opinion regarding the action of acids and alkalies on the pylorus, the results cannot well be explained by the action of these substances on this structure. It is not in the province of this paper to discuss at any length the action of acids and alkalies on the pylorus. It may be stated, however, that the acid-control theory of the pylorus suggested by Cannon (43), in 1898, is no longer tenable. It is known, for example, that the achlorhydric stomach empties faster than the normal stomach; furthermore, the work reported here, as well as the work reported by other investigators, show that alkalies in moderate doses administered with food hasten gastric emptying. Other objections can be raised; work reported by McClure, Reynolds and Schwartz (44) and by Thomas, Crider and Mogan (35) has shown that acid placed in the antrum of the stomach does not affect the tone of the pyloric sphincter. The work of many other investigators could be quoted giving further objections to the acid-control theory of the pylorus. There are too, some physiologists who believe that normally the pylorus plays a minimum role in the mechanism of gastric evacuation. It seems to the authors that it is untimely to suggest that the action of the pylorus is especially affected by the reaction of the gastric contents.

Some evidence has been presented (45) that the mechanisms controlling secretory and motor function

of the normal stomach, in response to a meal, must be identical. While this may hold in the case of normal stomachs, it certainly is not applicable in the case of achlorhydries, whose stomachs often empty even more rapidly than normal, or in ulcer patients, who may have marked retention in stomachs with a relatively high acidity, even in the absence of organic obstruction. However, if the mechanisms controlling secretory and motor function are identical in the normal stomach, it is logical that when acid is added to the gastric contents part of the need for secretory function is removed, so that less secretory work is done, and, concomitantly, the motor function may be somewhat decreased. Conversely, if alkali be added, then there is the stimulus for added secretory function, and, with the increase in secretory function necessary to produce optimum digestive conditions, there may also be an augmentation of motor function. While the above does not explain the ultimate mechanism involved, it does furnish a working hypothesis. It must be mentioned again, however, that some workers (42) feel that there is no definite correlation between gastric acidity and motility.

Several workers have studied the effect of acids and alkalies on excised gastric strips. Gorman, Dreier and Rehfuess (46) found that very high dilutions of hydrochloric acid inhibited or arrested the spontaneous contractions of strips from the pyloric antrum. Sodium bicarbonate or sodium citrate almost invariably restored the contractions abolished by acid, and often caused an increase in tone and contractions of otherwise untreated strips. McSwiney and Newton (47) also noted that alkalosis caused a rise in the tone of smooth muscle strips. Alvarez (48), working on the action of drugs on isolated strips from different parts of the bowel, reported that a 10 per cent sodium bicarbonate solution, for the main part, had a stimulating effect, whereas the main effect of hydrochloric acid was a depressant one. It is realized that Alvarez was working with strips of intestinal musculature rather than gastric musculature, but his work is in accord with the results obtained by the workers just mentioned, who used excised gastric strips.

It would seem from the evidence presented, that the action of acids and alkalies on isolated strips of gastro-intestinal musculature offer the most tangible evidence as to the mechanism of these substances on gastric motility in the intact animal. It is recognized, however, that results obtained with isolated segments of an organ may not be entirely similar to those obtained working with an intact animal. It is difficult to see, furthermore, how acids and alkalies in the amounts used in the work reported here, could materially affect the gastric musculature. It would be necessary for them to penetrate the gastric mucosa in significant amounts which seems unlikely.

We feel that the results obtained with di-sodium phosphate are of distinct interest. There is, of course, no carbon dioxide given off when this preparation is

ingested. Since the results are so similar to those obtained with sodium bicarbonate, it appears that alkalization alone is capable of stimulating gastric motility.

The results reported by Kussmaul (1), Jaworski (2), Binet and Lebon (18) and Carnot and Koskowski (27) that carbonic acid causes increased gastric motility is worthy of comment. It might be expected that this acid, although a weak one, would, like other acids, have a retarding effect. One important factor to be considered, however, is that the mechanical distension caused by the carbon dioxide gas could produce a greater efficiency of contraction of the smooth muscle fiber. Binet and Lebon postulated that if hydrochloric acid were absent in the gastric contents, sodium bicarbonate did not have its usual stimulating action since carbon dioxide was not liberated. This statement can be challenged since our work showed that di-sodium phosphate could by its alkalizing action alone produce an increase in gastric motility.

### SUMMARY

Gastric emptying time was investigated in a series of healthy young adults, known to have hydrochloric acid in their fasting gastric juice. The standard test meal consisted essentially of 15 grams of Quaker Farina, cooked to a constant volume with water; 50 grams of barium sulphate were added after the meal had cooled. The normal emptying time was ascertained by repeated fluoroscopic examination. There was considerable individual variation, but the emptying time of any individual remained remarkably constant from day to day.

It was found that a therapeutic dose of hydrochloric acid (100 cc. of a solution containing 2 cc. of diluted hydrochloric acid) produced an average delay of 9 per cent in the emptying time of the stomach in 9 subjects. This percentage delay was not statistically significant. A therapeutic dose of sodium bicarbonate (5 grams in 100 cc. water) was followed by an average decrease of 16.3 per cent in the emptying time of the stomach in 10 subjects; statistically this figure was highly significant. Di-sodium phosphate was studied, in an attempt to decide whether or not the hastening which followed administration of sodium bicarbonate was due to an alkalizing effect, or to a specific effect of carbon dioxide. A therapeutic dose of the phosphate was used (4 grams dissolved in 100 cc. water); it produced an average decrease of 17.1 per cent in the gastric emptying time of three subjects. We interpret this as meaning that the action of alkali alone is capable of stimulating gastric motility.

Possible mechanisms to account for the effects produced by the acid and alkali are presented.

A review of the literature of the effects of acids and alkalies on the stomach is given.

Lastly, we feel that quantitative evidence as to the effects of therapeutic doses of commonly used acids and alkalies on the motor response of the normal stomach to a physiologic meal has been presented.

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## Urinary Amylase: Its Estimation and Significance\*

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IN the literature one finds considerable controversy concerning the clinical value of urinary amylase determinations. A consideration of the various points at issue reveals some of the reasons for differences of opinion. The exact origin and nature of amylase are not definitely established, and it is also recognized that methods for determining the quantity of amylase display certain discrepancies and lack of uniformity. Further experimental study is therefore indicated.

The presence of a "diastatic ferment" in urine was first recognized by Cohnheim (1) in 1863. Wohlge-muth (2), in 1908, attempted to establish a uniform method for determining the quantity of enzyme in a given specimen of urine. In 1918 Fearon (3) pre-

sented a very thorough and critical review of the "amylolytic properties of urine" and he concluded that "the whole question of urinary amylases, their occurrence and significance, is by no means settled and remains little more than a clinical curiosity in many hospitals." Since then, considerable data have accumulated and several methods for estimating the quantity of enzyme have been proposed, but the subject has not been clarified to any great extent.

### ORIGIN OF AMYLASE

Amylase has been found in vegetable cells which contain starch and in saliva, blood, pancreatic secretion, feces, liver, muscle, lungs and possibly may exist in other animal tissues. While it is definitely established that its presence in the animal is fairly wide-spread, it has not been definitely demonstrated whether it originates solely from one or from several sources.

Although it is generally agreed that urinary amylase is derived from the blood, two opposing views

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are current with respect to the origin of blood amylase. There are those who believe that it is exclusively pancreatic in origin and others maintain that it originates in part, at least, in the liver and possibly in other tissues.

The proponents of the first theory point out that Wohlgemuth (4) (1908), Davis and Ross (5) (1921), Zucker, Newburger and Berg (6) (1932), Reid, Quigley and Myers (7) (1933) and others, uniformly showed that removal of the pancreas resulted in a decrease in blood amylase. The rise in the blood amylase following pancreatic duct ligation as recorded by Wohlgemuth (4) (1908), Gould and Carlson (8) (1912), Elman, Arneson and Graham (9) (1929), Zucker (6) (1932), Johnson and Wies (10) (1932) and many others, is cited as additional support for the hypothesis of the pancreatic origin. Furthermore, Elman (11), Bernhard (12) and McCaughan (13) have noted that in certain diseases involving the pancreas, particularly if pancreatic duct occlusion occurs, there is an increase in the blood amylase, while if acinar tissue is destroyed, a low blood amylase is found.

Antopol, Schiffrin and Tuchman (14) reported an increase in the blood amylase of dogs, following administration of acetyl-beta-methylcholine chloride; but, after total pancreatectomy (15), they were unable to elicit any response subsequent to the use of this same preparation. Zucker, Newburger and Berg (6), and Davis and Ross (5) noted a fall in the blood amylase following chloroform anesthesia. Davis and Ross ascribe this drop to the effect of chloroform on the pancreas, since they failed to get a decrease in blood amylase in depancreatized dogs given chloroform anesthesia, even though the liver showed damage.

Data to support the view that blood amylase is in part, at least, of liver origin are also available. Carlson and Luckhardt (16) found no change in blood amylase in three cats following removal of the pancreas. The same experience was recorded by Bainbridge and Beddard (17) in one cat and by Milne and Peters (18) in several dogs. Gould and Carlson (8) and Reid and Myers (19) found a persistence of amylase in the blood after the original drop, following complete removal of the pancreas. The decrease in blood amylase when liver damage is present, as borne out by the work of Davis and Ross (5) (1921), Zucker (6) (1932), Somogyi (20) (1934), Rachmilewitz (21) (1938), and Cajori and Vars (22) (1938), suggests a liver origin for the amylase in the blood. Elman (9) states that some investigators report a greater amount of amylase in the blood leaving the liver, than that entering it and that they believed this indicative of hepatic origin of the enzyme.

Cohen (23) found a fall in the blood amylase after the administration of adrenalin, morphine and insulin, and suggested that amylase is recalled to the liver to cause greater glycogenolysis. Cohen (23) and Myers (24) detected an increase in liver amylase coincident with a fall in the blood amylase. Liver amylase, as an important factor in the normal glycogen-glucose change in the liver has been discussed, amongst others, by Rosenfeld (25) and Lessor (26). However, the recent work of Cori and Cori (27), questions the significance of liver amylase in glycogenolysis.

## THE NATURE OF AMYLASE AND THE CONDITIONS WHICH GOVERN ITS ACTION

In addition to the controversy which exists, concerning the origin of amylase, some workers believe that there is more than one type of amylase in the animal. Crandall (28) suggested that we refer to the amylase which is responsible for reducing sugar as the "saccharogenic amylase" and to the enzyme which causes changes in viscosity as the "liquefying amylase." Fearon (3) showed a different optimum pH for the amylase in saliva and that in urine. Eadie (29) and Davenport (30) found that liver extracts exhibited optimum amylase activity at two pH levels, a fact which they interpreted to indicate the presence of two enzymes. Elman (11) and his colleagues used 6.8 as the optimum pH for amylase in blood. Schmidt (31) and his co-workers recorded 6.8 to be the optimum pH for amylase in duodenal fluid, while Fearon (3) reported that 7.2 to 7.4 was optimum pH for urinary amylase, further supporting the view that there is more than one amylase. Takano (32) studied the amylase action of the pulmonary tissue and reported that the behavior of pulmonary amylase to halogen-salts is quite different from swine pancreas and human saliva. Chesley (33) remarked that the kinetics of amylase action were difficult to measure, for there was some evidence to show that one is measuring the activity of a mixture of two or three distinct enzymes.

That amylase or the amylases are of the nature of a protein has been advanced by Sherman (34). Cook (35) studied malt and pancreatic amylases under certain specified conditions for the temperature range of 20° to 70° C. and found that pancreatic amylase was completely destroyed in fifteen minutes, heating at 50°. Cook is in accord with the view of Sherman that the destruction of the enzyme by heat may be in the nature of coagulation of protein.

## EXPERIMENTAL STUDIES

The Schmidt, Greengard and Ivy (31) modification of the Willstater test was first studied. Early experimentation, however, indicated that while this method might be suitable for measuring the amylase content of duodenal drainage and pancreatic juice, it was not equally applicable to urine. The difficulties encountered were chiefly due to a persistent high blank and to the small difference between the blank and incubated specimen. Studies were conducted on unaltered, filtered, boiled, autoclaved and frozen samples without appreciable effect on the blank. It was then deemed necessary to resort to some form of treatment which would eliminate the interfering nitrogenous and reducing substances from the urine.

Clarification of the urine was attempted by treatment with powdered basic lead acetate, norite, zinc sulphate and sodium hydroxide, Lloyd's reagent, colloidal iron, West's (36)  $\text{HgSO}_4\text{-BaCO}_3$  procedure and various combinations of the above. It was found that the blank could be reduced considerably and that the  $\text{HgSO}_4\text{-BaCO}_3$  procedure plus Lloyd's reagent yielded the most satisfactory results. The Willstater test was again employed; and while the blank was appreciably diminished, the amounts of reducing material in the blank and in the hydrolyzed specimen were frequently nearly alike and, therefore, a more accurate method

had to be selected. The sensitive Shaffer-Hartmann (37) procedure was found to fulfill this requirement.

### PROCEDURE

The urine is filtered and placed in either a water bath or incubator at 37° C. In the meantime a fresh 2% soluble starch solution is prepared and buffered to a pH of 6.8 with a 0.2 M phosphate and 0.2 M NaCl solution as outlined by Schmidt (31) and his co-workers. The soluble starch was prepared by the method of Small (38).

Ten cc. of buffered starch solution are pipetted into each of two 250 cc. Erlenmyer flasks. It might be mentioned that contamination with saliva must be avoided. One flask is placed either in a constant temperature water bath or in an incubator at 37° C. and allowed to remain until the flask and contents have assumed a temperature of 37°. During this time 10 cc. of urine are added to the other flask and immediately followed by 15 cc. of the  $\text{HgSO}_4\text{-H}_2\text{SO}_4$  mixture recommended by West (36). This latter mixture is to serve as the blank. When the flask and contents in the incubator have assumed the desired temperature, 10 cc. of urine are added and allowed to digest for exactly 15 minutes. (It is possible that when dealing with

to the Shaffer-Hartmann (37) method. The quantity of reducing sugar formed by the enzymatic action is in turn calculated by subtracting the amount of reducing material in the blank from that of the digested specimen. For convenience the end product is expressed in terms of glucose.

### URINARY AMYLASE UNDER VARIOUS CONDITIONS IN HEALTH

Before other studies had been undertaken, the stability of amylase in urine was tested by preserving the specimen with toluene and refrigeration. Daily tests were conducted for a period of one week and the enzyme was found to remain active. However, diminished potency was noted after five to six days. Toluene, as a preservative, had no effect on amylase activity. The filtrates containing the reducing sugar were also tested and there was no appreciable change

TABLE II

*The 24-hour range of amylase excretion in urine of normal individuals*

Subject Number	Amylase Activity for 10 cc. Morning Urine	Amylase Activity for 10 cc. 24 Hour Urine	Amylase Activity for Entire 24 Hour Urine	24 Hour Volume cc.
1	8.8	8.3	953	1145
2	9.1	5.1	586	1150
3		7.6	795	1040
4		1.8	283	1517
5	7.1	3.0	422	1380
6	6.8	4.7	725	1295
7		5.1	849	1665
8	6.6	4.7	497	1045
9		7.6	785	1040
10	5.6	4.9	690	1400
11	7.3	2.2	264	1195
12	4.9	5.4	701	1290
Range	4.9 to 9.1	1.5 to 8.3	264 to 953	1040 to 1665
Average	6.9	5.0	629	1263

TABLE I

Subject Number	pH of Urine	Amylase Activity* for 24-Hour Urine
14	5.0	2141
15	5.4	1433
13	5.8	1338
15	6.2	1093
16	6.2	764
20	6.5	1224
19	7.9	1050

\*Amylase activity expressed in mms. of glucose for the amount of reducing material produced by the amylolytic activity of urine studied as described under "Procedure."

samples of urine that exhibit very slight amylolytic activity, one can increase the efficiency of the test either by using a larger sample of urine or by allowing the incubation to proceed for a longer period of time). At the end of this time the enzymatic activity is interrupted by the addition of 15 cc. of West's  $\text{HgSO}_4\text{-H}_2\text{SO}_4$  mixture. A pinch of Lloyd's reagent is then added to each flask, and thorough shaking is instituted.

To each flask 35 grams of  $\text{BaCO}_3$  are added and then 50 cc. of distilled water. The mixture is stoppered and agitated until  $\text{CO}_2$  ceases to be produced. The material is now filtered, and the filtrate acidified by the addition of one drop of concentrated  $\text{H}_2\text{SO}_4$ . The mercury is eliminated by saturating the filtrate with  $\text{H}_2\text{S}$ , and the excess  $\text{H}_2\text{S}$  is driven off by bubbling air through the solution. This solution in turn is filtered, and the filtrate rendered alkaline by the addition of a few crystals of  $\text{Na}_2\text{CO}_3$ , Phenol-red being employed as the indicator.

The amount of reducing material in 5 cc. aliquots (a smaller quantity of the filtrate should be used if large amounts of reducing materials are present) of the slightly alkaline filtrate is determined according

in the amount of reducing sugar after remaining in the refrigerator for three days.

The efficiency of the buffer solution was determined by estimating the amylase activity of urines with a different pH. Seven urine samples were tested and it was found that the original pH of the urine, before buffering, had no relation to the amount of amylase activity. The results are shown in Table I.

A known amount of Maltose was added to some starch-urine samples in order to ascertain if the West reagent influenced recovery. Satisfactory recoveries were obtained with a maximum error of  $\pm 5\%$ .

The reports from different investigators reveal considerable variation in normal values for urinary amylase. In an attempt to determine the reason for inconsistencies in normal values, a group of healthy individuals was selected and they were studied from

the standpoint of the 24-hour range of amylase excretion, the effect of restricting and forcing fluids on amylase output, the variation in rate of amylase excretion during a 24-hour period, the relation between the concentration of urine (specific gravity), volume and amylase content, and the effect of diet on excretion or formation of urinary amylase.

*The 24 hour range of amylase excretion for normal individuals*

Twelve 24-hour urines were examined, also 10 cc. of the morning urine were analyzed separately. The morning urine was analyzed separately for the purpose

TABLE III  
*Amylase activity for entire 24-hour urine*

1.	607, 497, 671
2.	795, 428, 517, 306, 436
3.	405, 581, 563, 264

of determining if 24-hour collections could be avoided. It is noted from Table II that there was considerable variation in different individuals. While the degree of variation was approximately the same whether one studied the entire 24-hour urine or only the morning urine, the morning urines had higher amylase activity per 10 cc. than the 24-hour samples. The ranges and averages for 10 cc. of urine and for the 24-hour excretions are given in the table. Since the variation in different individuals is rather marked, it was decided to study the variation for the same individual. Three

24-hour samples were studied from one individual, five from another and four from still another, with results shown in Table III.

Thus it appears that variations are not only present in different individuals, but in the same individual on different days. This is in accord with the results of Gray and Somogyi (39).

*The effect of restricting and forcing fluids on amylase output*

Six of the normal individuals previously studied were placed on restricted fluid intakes and were requested not to exceed 1,000 cc. The remaining six were asked to force fluids as much as possible. The results are tabulated in Table IV. Restricting or forcing fluids seemed to cause no greater variations than occurred under normal conditions. This being true, there was more enzyme in the concentrated samples and less in the diluted specimens. In this respect it would seem that a specimen taken at random would not yield reliable results.

*The rate of amylase excretion during a 24-hour period*

The 24-hour urine was collected in three separate periods of 8-hours each. Collections were made from 7 a.m. to 3 p.m., 3 p.m. to 11 p.m., and 11 p.m. to 7 a.m. Five such collections were made from three different individuals who had previously been studied. Table V shows that the rate of excretion was not uniform throughout the 24-hour period. There was a tendency for a greater excretion from 7 a.m. to 3 p.m. Three showed the slowest rate of excretion from 3 p.m. to 11 p.m. and in two there was a minimum of amylase excreted from 11 p.m. to 7 a.m. Since the time of rapid

TABLE IV  
*The effect of restricting and forcing fluids on amylase output in urine*

Normal Intake*			Force Fluids		
Subject Number	Amylase Activity for 24 Hour Urine	Amylase Activity for 10 cc. Morning Urine	Amylase Activity for 10 cc. 24 Hour Urine	Amylase Activity for Entire 24 Hour Urine	24-Hour Volume cc.
1	953	3.5	3.0	942	3050
2	586	5.9	2.8	780	2700
3	795	3.7	1.5	443	2900
4	283	5.1	1.8	617	3300
5	422	3.9	1.1	725	6100
6	725	3.4	2.7	1093	4020
Range		3.4 to 5.9	1.1 to 3.0	617 to 1093	2700 to 6100
Average		4.2	2.2	766	3685
Normal Intake*			Restrict Fluids		
7	849		5.2	714	1855
8	497	9.5	8.5	607	715
9	785	8.5	8.1	836	1025
10	690	9.3	8.5	705	830
11	264	12.2	8.1	563	690
12	701	6.4	7.4	710	950
Range	264 to 953	6.4 to 12.2	5.2 to 8.5	563 to 836	715 to 1855
Average	629	9.2	7.6	689	927

\*Figures for 10 cc. of morning urine and 10 cc. of 24-hour urine for the normal intake studies are given in Table II.

or slow excretion varied in the same individual, it can be said that there is no definite relation between rate of excretion of amylase and time of the day. Fearon (3) reported that the maximum amount is found following meals.

*The relation between the concentration of urine (specific gravity), volume and amylase content*

This study appeared advisable, for if a definite relation could be shown between the specific gravity and the amylase content, 24-hour collections would be un-

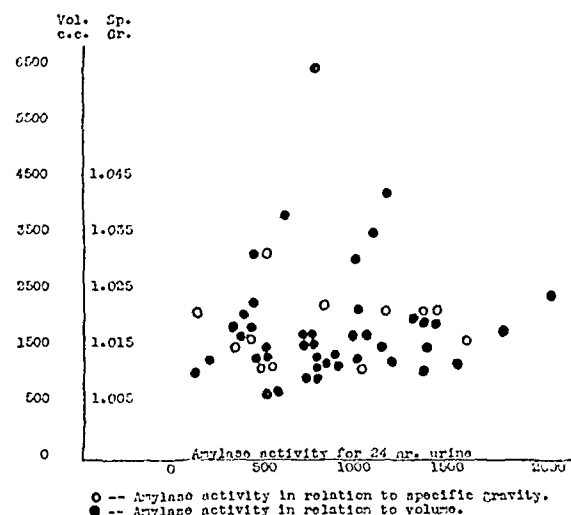


Fig. 1. The relation between the concentration of urine (specific gravity), volume and amylase content.

necessary. It will be noted, however, from Fig. 1 that while the specimens with high specific gravities tend to possess greater hydrolyzing powers, the relation is not absolute nor invariable and this procedure is, therefore, impractical. Also, under the various conditions when glycosuria is found, this entire relationship is destroyed. The inadvisability of trying to avoid 24-hour collections by making a correction for the specific gravity is better shown if graphed by plotting the log of the specific gravity against enzyme activity in terms of milligrams of glucose. Fig. 1 also shows

that there is no definite relation between the total volume and the total amylase content of a 24-hour sample of urine.

*The effect of diet on excretion, or formation, of urinary amylase*

Table VI records the data from these experiments. Since the normal variation is so great, the results obtained would indicate that diet has no appreciable effect on the amount of amylase in urine. The many discrepancies in the literature support the belief that diet has very little effect if any. Some of the figures in this group of normals are slightly higher than those enumerated in Table II. With some exceptions, the members of this group were slightly younger. One would hardly be justified in assuming that the slight difference in age would account for the increased output. As a matter of fact, those of a corresponding age in Table II were in the lower bracket.

Gould and Carlson (8) found no change in blood amylase in dogs that had been on a 10-day fast. Milne and Peters (18) detected no change in dogs from fasting or a meat or a sugar diet. Lewis and Mason (40) reported slight decreases in blood amylase in men after a fat-protein meal and a slight rise after glucose administration. Brown and Greene (41) reported a rise after carbohydrate feeding coincident with blood sugar rise. Reid and Narayana (42) found a slight decrease in blood amylase after food or glucose ingestion. Wohlgemuth (2) found a high urinary amylase after fasting. Leo (43) studied a professional faster and was able to show an increase in the ferment in the urine from day to day during the periods of starvation.

### URINARY AMYLASE IN DISEASE

After having considered the variation in quantity of amylase in the urine under different conditions in health, studies were conducted on patients with different diseases. However, in evaluating the material to be presented, one should keep in mind that the investigations conducted upon normal individuals revealed that the range of amylase excretion during a 24-hour period, varies tremendously in different individuals and in the same individual from day to day. It should also be borne in mind that the great variation in the 24-hour output of amylase in normals is not related

TABLE V  
*The rate of amylase excretion during a 24-hour period*

Subject Number	Volumes and Amylase Activities of Urines Collected During Consecutive 8-Hour Periods						Total Amylase for 24 Hours	Total Vol. cc.
	7 A.M. to 3 P.M.		3 P.M. to 11 P.M.		11 P.M. to 7 A.M.			
	Amylase	Vol. cc.	Amylase	Vol. cc.	Amylase	Vol. cc.		
3	201.8	475	153.2	490	132.6	300	517	1265
3	192.7	610	78.5	385	157.0	220	428	1415
11	192.7	180	36.7	40	174.9	147	405	367
11	199.0	280	163.7	205	219.9	230	581	715
8	338.9	400	295.5	265	127.1	310	671	975



TABLE VI  
The effect of diet on excretion, or formation, of urinary amylase

Subject Number	Urinary Amylase for 24 Hours Before Diet	Nature of Diet	Urinary Amylase for 24 Hours After Diet	
13	1107	Normal diet containing large doses of $\text{NH}_4\text{Cl}$	1st day	2141
15	1296	Normal diet containing a large quantity of prunes	2nd day	1233
17	449	Normal diet plus large doses of ascorbic acid		1333
19		Normal diet containing large doses of sodium citrate		102
20		Normal diet containing a large quantity of oranges		1050
14	1561	Fasting		1224
		Fasting	1st day	1093
			2nd day	1433
16	513	High protein		784
3	428 to 795	High carbohydrate		306 to 436
18		Carbohydrate, fat		930 to 831

to diet or fluid intake, and that the rate of excretion is not uniform throughout the 24-hour period.

As we turn to study urinary amylase in disease, we are confronted with the problem of classifying the cases according to severity and duration of the particular organic condition under consideration. There is no reliable criteria to assure us that every case of toxic goitre, liver disease, etc., is of the same severity and there is no means of measuring the effect of the duration of the disease upon other body tissues. Of necessity, therefore, a group of patients representing any particular disease will include different grades of severity and duration. This may account for some of the inconsistencies.

*The 24-hour range of amylase excretion in patients with diabetes mellitus*

When considering this group we must take into account not only the severity and duration of the disease, but also the type, whether primarily pituitary or pancreatic and the effect of varying dosage of insulin. Several workers have shown that the amount of blood amylase can be influenced by varying the dose of insulin.

The patients selected for this study all had persistent hyperglycemia and glycosuria, no clinical evidence of any other disease being present. Samples were not collected, however, until the hyperglycemia and glycosuria had been controlled by diet and insulin.

TABLE VII  
The 24-hour range of amylase excretion for patients with diabetes mellitus

Diagnosis	Fasting Blood Sugar Before Treatment	Fasting Blood Sugar After Treatment	Specific Gravity	Vol. cc.	Amylase Activity for 10 cc. Urine	Amylase Activity for 24 Hour Urine
Diabetes Mellitus	141	104	1.008	1650	16.8	2772
"	150	114	1.010	1200	3.5	420
"	150	108	1.008	1275	1.8	238
"	160	125	1.013	1250	2.7	340
"	160	100	1.008	1900	2.5	484
"	173	107	1.010	1100	7.1	735
"	175	140	1.020	1500	3.0	459
"	176	125	1.010	1650	5.7	953
"	176	115	1.010	1200	2.2	306
"	180	116	1.014	1100	8.9	430
"	190	100	1.009	2300	5.4	1311
"	200	140	1.015	800	4.4	353
"	205	120	1.011	980	2.2	216
"	220	110	1.010	550	7.6	420
"	220	130	1.018	1300	8.3	1082
"	226	118	1.025	600	2.5	153
"	231	150	1.020	800	1.7	136
"	250	120	1.008	2120	1.7	360
"	285	112	1.020	950	0.6	66
"	329	160	1.026	480	7.3	553

Non-standardized diabetics are difficult to study because of the large quantities of glucose in the urine, a condition necessitating great dilutions or fermentation of the excess sugar.

The data from 20 patients may be found in Table VII. The 24-hour excretion varied considerably. Ten samples ranged from 65 to 360, and the other ten ranged from 420 to 1311, excepting one, which was 2772. It is possible that the two groups represent different forms of diabetes, but evidence to substantiate this thought is lacking. There was no definite relation between the amylase output and the severity of the diabetes, as indicated by the fasting blood sugar prior to institution of treatment. However, the greatest output was in the case which displayed the lowest blood sugar. Leo (43) and Bendersky (44) reported high values for diabetics. Lepine (45), Fearon (3) and Wohlgemuth (2) found the yields to be lower. Clark (46) was unable to detect any enzyme in six cases of diabetes.

It will be noted that there is considerable variation in different individuals in the study herein reported, which is in keeping with the variation in the results from different laboratories. The lack of uniformity may be attributed to differences in the types and severity of the disease. Also it is very likely that some of the reports included both treated and untreated cases.

*The 24-hour amylase output in a group of patients with liver disease*

Twenty patients were studied, practically all of

whom had hepatomegaly without other associated diseases. Most of the patients were jaundiced. All of the patients revealed abnormal liver function, as determined by the serum bilirubin, urobilinogen, the galactose test, bromsulphthalein excretion or the Takata-Ara test. The underlying pathology in most instances, as observed clinically, was some form of cirrhosis or toxic liver damage, or metastatic carcinoma; in some cases there was uncertainty of the actual disease. Results of amylase determinations recorded in Table VIII varied from zero (no difference between the blank and digested specimen) to 2720. Five ranged from zero to 360; 14 from 481 to 1518, and one reached 2720. The low figures were obtained in those cases exhibiting evidence of considerable hepatic insufficiency. It would appear that amylase output is diminished if the liver is involved sufficiently. There does not, however, seem to be any definite relation between the serum bilirubin level and the amount of amylase excreted. Cajori and Vars (22), Rachmilewitz (21) and Somogyi (20) have shown a diminished blood amylase when there was distinct liver damage.

*The urinary amylase in patients with nephritis*

Data from the ten patients studied will be found in Table IX. Some had azotemia and all had pathological ingredients in the urine at one time or another. Impairment of urea clearance or dye excretion was manifested by all. The specific gravity varied. Amylase determinations varied from 261 to 897 and there was no parallel between the blood urea nitrogen or urea

TABLE VIII  
*The 24-hour amylase output in a group of patients with liver disease*

Diagnosis	Sp. Gr.	Vol. cc.	Mgs. % Serum Bilirubin	Amylase Activity for 10 cc. Urine	Amylase Activity for 24 Hour Urine
Stone in common duct—large liver—J*		1022	10.2	10.4	913
Cholelithiasis with hepatomegaly—J	1.021	810	5.0	5.9	491
Carcinoma of liver—J	1.034	275	5.5	0.6	14
Hepatomegaly with jaundice	1.010	2290	5.2	6.6	1518
Catarrhal jaundice	1.011	2245	5.0	4.4	992
Catarrhal jaundice	1.020	960	5.0	9.3	919
Myelogenous leukemia-hepatomegaly—J	1.011	1970	4.2	6.1	1205
Large liver—J	1.020	1000	4.2	9.5	952
Carcinoma of common duct—large liver—J	1.012	1200	3.5	.0	0
Portal cirrhosis—J	1.030	370	3.5	17.5	647
Portal cirrhosis—J	1.013	2239	3.0	6.1	1350
Portal cirrhosis—J	1.011	1450	2.5	1.0	147
Metastatic carcinoma	1.008	1600	2.2	17.0	2720
Metastatic carcinoma—J	1.018	400	2.1	1.7	63
Portal cirrhosis	1.020	1650	0.8	6.1	1037
Portal cirrhosis	1.010	900	0.5	4.0	360
Portal cirrhosis	1.003	1500	0.4	4.3	654
Portal cirrhosis	1.012	1750	0.3	5.6	955
Portal cirrhosis		1330	0.2	8.0	1057
Large hemangioma of liver	1.012	2235	0.2	5.2	1172

\*Capital J following the diagnosis indicates that the patient was jaundiced.

TABLE IX

*The urinary amylase in patients with nephritis*

Type of Glomerular Nephritis	Sp. Gr.	Vol. cc.	B.U.N.	% Urea Clearance	Microscopic	Amylase Activity for 10 cc. Urine	Amylase Activity for 24 Hour Urine
Nephrotic form	1.015	1050	60	14	Casts, Alb.	5.2	553
Nephrotic form	1.028	..	55	21	Casts, RBC	8.8	...
Chronic, diffuse	1.040	2400	30	68	Casts, RBC	3.7	897
Nephrotic form	1.020	...	22	60	Casts, RBC	17.0	...
*Benign arteriolo-nephrosclerosis	1.010	790	20	58	Casts, Alb.	6.8	189
*Subacute, diffuse	1.030	480	16	40	Casts, RBC	13.4	644
Chronic, diffuse	1.010	1100	15	75	Casts, Alb.	2.3	261
*Acute, diffuse	1.027	304	14	77	Casts, RBC	10.3	311
Chronic, diffuse	1.007	..	12	80	Casts, Alb.	1.5	...
**Acute, diffuse	1.017	790				6.9	550

\*12 hour collections

\*\*Also mild diabetic.

clearance and the excretion of amylase. In three cases only 12-hour collections were made with results 311, 189 and 644. These figures are not at great variance from the normals. Fearon (3), Wohlgemuth (2), and Gray and Somogyi (39) reported low findings in cases with renal disease. Hewlett (47) states that the determination of urinary amylase used to be employed as a renal function test. Geyelin (48) compared the excretion of amylase with that of phenolsulphonethalein and found that the two varied together in nephritis. Fitz (49) compared the non-protein nitrogen of the blood and the amylase excretion in experimental uranium nephritis, and found that with the

onset of the nephritis the excretion of amylase falls and the non-protein nitrogen of the blood rises and that with recovery the reverse relationship occurs. If this finding can be confirmed, it will be necessary to do urinary amylase determinations in all cases exhibiting an elevation of the blood amylase to determine if it is increase formation of amylase or retention.

Here again it is difficult to speak of renal disease as an entity, for there is no reason to expect that a severe, acute, diffuse glomerulonephritis with nitrogen retention and oligo or anuria should give the same results as a well-compensated case of chronic nephritis with polyuria, or a case of nephrosis.

TABLE X

*The urinary amylase in patients with diffuse, toxic thyroid disease*

Diagnosis			Basal Metabolic Rate	Specific Gravity	Vol. cc.	Amylase Activity for 10 cc. Urine	Amylase Activity for 24 Hour Urine
Diffuse	Toxic	Thyroid	Plus 82	1.009	1320	4.5	605
"	"	"	" 80	1.024	630	5.5	353
"	"	"	" 65	1.022	810	9.0	729
"	"	"	" 60	1.022	865	2.5	220
"	"	"	" 50	1.010	1080	4.2	459
"	"	"	" 48	1.020	320	9.5	306
"	"	"	" 40	1.012	1230	4.4	550
"	"	"	" 40	1.010	2075	2.7	564
"	"	"	" 39	1.024	1500	2.5	382
"	"	"	" 38	1.020	720	9.5	680
"	"	"	" 36	1.024	2300	2.8	644
"	"	"	" 34	1.024	400	11.3	452
"	"	"	" 32	1.020	1320	6.2	830
"	"	"	" 32	1.018	790	5.1	404
"	"	"	" 28	1.020	1130	4.5	518
"	"	"	" 28	1.010	390	6.1	238
"	"	"	" 24	1.022	3650	2.1	785
"	"	"	" 18	1.022	1710	2.4	420
"	"	"	" 18	1.010	2850	1.5	436
"	"	"	" 12	1.006	875	9.6	845

*The urinary amylase in patients with diffuse, toxic thyroid disease*

Twenty patients were studied, all of whom had the clinical picture of diffuse, toxic thyroid disease, which was confirmed by the laboratory findings. The urinary amylase excretion reported in Table IX ranged from 220 to 845. It would appear that this is not a very marked departure from the normal. Some of the lower figures, e. g., 220, 238, 306, 353 and 382 were obtained in the more toxic cases. Some of the higher figures, however, were from patients with an equal degree of toxicity as determined by the B. M. R. and clinical signs. It does not appear that there is any relation between the B. M. R. and the amount of amylase found in the urine. This, however, might be influenced by the duration of the disease prior to therapeutic measures. Bartels (50) has demonstrated that a large percentage of patients with hyperthyroidism have impairment of liver function, based on the hippuric acid excretion test. The degree of hepatic impairment being directly proportional to the toxicity of the hyperthyroidism. It would appear that any diminution in amylase excretion would depend upon the degree of secondary liver involvement.

*The urinary amylase in patients suffering from diseases of the pancreas*

Eleven patients were studied. The diagnosis as set forth in Table XI was established in each instance at operation. The range in this group was from 607 to 4870, somewhat higher than in any of the preceding groups. There were three cases of acute pancreatitis with edema and hemorrhages of the gland, distention of the capsule, and necrosis of the surrounding adipose tissue. One case was studied on the 1st, 2nd and 3rd postoperative days with the following results: 974, 1372 and 1138. The second case was studied on the 1st and 5th postoperative days with the following results: 3870 and 1356, respectively. The third case

presented too much sugar in the urine for satisfactory determinations. However, the serum lipase was normal and the serum amylase was low. A case with a cyst and necrosis of the pancreas, studied the 2nd postoperative day, was 858. Another case of pancreatic cyst following a gunshot wound yielded 3000 on the first postoperative day and 1154 on the second postoperative day. A third case of pseudo-cyst of the pancreas with drainage, following an operation for acute pancreatitis six months previously, showed 787. Three cases of carcinoma of the pancreas yielded 3378, 2720 and 652. A case of pancreatic apoplexy showed 1286 on the second postoperative day and 607 one month later.

While the highest figures obtained were in the group with pancreatic pathology, the results were not consistent. It has been shown that following experimental pancreatic duct obstruction, urine amylase rapidly rises, but returns to normal within a comparatively short time. Some of the inconsistencies no doubt were due to the interval which elapsed from the onset of the disease to the time the studies are conducted. Also the extent of involvement may influence the results, for Elman has shown that the serum amylase is reduced if destruction of the acinar tissue is present. This latter factor is also to be considered in cases with cysts or carcinoma of the pancreas. The time interval factor, however, should not be very important in this latter group. The location of the cyst or carcinoma in relation to the pancreatic ducts may be of importance in regard to the amount of amylase excreted in the urine. In our discussion of the origin of amylase, current views in regard to the effect on amylase of pancreatectomy, pancreatic duct ligation, acute pancreatitis, etc., were presented.

### SUMMARY AND CONCLUSIONS

A review of current views concerning the origin of urinary amylase, the nature of amylase, the different

TABLE XI

*The urinary amylase in patients suffering from diseases of the pancreas*

Diagnosis	Specific Gravity	Vol. cc.	Amylase Activity for 10 cc. Urine	Amylase Activity for 24 Hour Urine
Cyst and necrosis of the pancreas	1.032	1018	7.1	858
Traumatic pancreatic cyst	1.010	1000	30.0	3000
Traumatic pancreatic cyst 2 days later	1.022	1050	10.7	1154
Acute pancreatitis		540	19.8	974
Acute pancreatitis 1 day later		1075	12.7	1372
Acute pancreatitis 2 days later		1860	6.1	1138
Carcinoma of the pancreas	1.010	1440	23.4	2378
Pancreatic apoplexy	1.020		17.5	
Pancreatic apoplexy next day	1.020	890	14.4	1286
Pancreatic apoplexy 1 month later	1.010	470	12.9	607
Carcinoma of pancreas	1.008	1600	17.0	2720
Acute pancreatitis	1.020	1500	32.4	4870
Acute pancreatitis 5 days later	1.006	1400	9.7	1356
Carcinoma of pancreas	1.020	1200	5.4	652
Carcinoma of pancreas		Glycosuria too marked		
Acute pancreatitis		Glycosuria too marked		
Pseudo-cyst of pancreas	1.008	960	8.2	787

phenomena encountered with the different methods for measuring the enzyme, and the factors which govern amylase action has been presented. In an attempt to clarify this discussion, a reliable method for estimating urinary amylase was developed and studies were conducted under various conditions in health and in disease.

A group of normals was studied in order to obtain normal ranges for amylase excretion during 24 hours, and this same group was restudied to determine the effect on the excretion or formation of amylase by restricting and forcing fluids, varying the diet and changing the pH of the urine. Also the rate of amylase excretion during a 24-hour period, and the relation between the concentration of urine (specific gravity), volume and amylase content were determined.

It was noted that the normal range varied considerably and that the foregoing factors had very little influence on the rate of urinary amylase excretion. While a more concentrated specimen of urine exhibited greater hydrolyzing qualities, the 24-hour collections showed the same variation whether dilute or concentrated. However, a sample of urine collected at random is apt to yield misleading information, for there can be considerable variation in the amount of amylase found in 10 cc. specimens of urine from the same individual taken at different periods of the day, or on alternate days. The rate of amylase excretion is not uniform throughout the 24-hour period. Diet had very little influence on the amount of urinary amylase.

The quantity of urinary amylase was determined in patients with different pathological conditions. Groups of diabetics, nephritics, patients with diffuse toxic thyroid disease, hepatic disease and pancreatic disease

were studied. High and low figures were obtained in each group. It is possible that this variation depends upon different stages of the respective disease. The highest figures were obtained in patients with pancreatic disease; the findings, however, were not consistent. Although there occasionally is a greater amount of urinary amylase in diseases of the pancreas, a low amylase does not rule out pancreatic disease and conversely a high amylase is not pathognomonic of pancreatic disease. It is difficult, therefore, to evaluate properly the laboratory report from a clinical standpoint, particularly when confronted with the possibility of an acute pancreatic catastrophe. There is a tendency for a diminished output of urinary amylase in cases with severe liver damage. The relationship between urinary amylase and renal function is not definitely shown by this study.

As a result of the great variation in normals and the lack of consistent findings in the diseases studied, we agree with von Benczur (51) that the routine determination of urinary amylase for diagnostic purposes does not yield significant results and should be discouraged.

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## II. The Biliary Pigment Curve During the Secretin Test

### Its Diagnostic Significance in the Non-Functioning Gall Bladder\*

By

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and

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IN a previous communication (1) we have described the effect of an intravenous injection of secretin upon the flow of pancreatic juice in man. Using a double gastro-duodenal tube under gentle suction the pure duodenal secretions were collected without admixture of the acid gastric juices. The injection of 0.5 mg. of secretin per kilogram of body weight gives rise, in the normal individual, to a flow of pure pancreatic juice rich in bicarbonate and the enzymes: diastase, trypsin and lipase. The total volume of flow varies between 150 and 250 cc. during the 80 minute test period. The bicarbonate concentration of this juice rises rapidly to as high as 96 to 126 millequivalents.

The volume of flow, the concentration of bicarbonate and the total output of enzymes per given time in the normal individual constitute a standard which is utilized as a clinical test of pancreatic function. In pathologic states involving the pancreas the total volume of secretion, bicarbonate concentration and enzyme output may be either individually or simultaneously affected.

In the present communication we wish to report our studies of the bile pigment concentration curve in the various samples of duodenal juice recovered during the secretin test. It has been shown that secretin, in addition to the stimulation of the external secretion of the pancreas, also possesses a choleric effect causing an appreciable flow of liver bile. Agren (2) has shown in the experimental animal that when the cystic duct is ligated and the common duct is cannulated the injection of secretin results in a marked increase in the flow of liver bile. This is in direct proportion to the dose of secretin used. With an injection of 0.05 mg. of secretin in a cat the liver bile flow increased from 8 to 30 drops per hour. In man the quantity of liver bile secreted during the test period of 80 minutes may reach as high as 60 to 80 cc. Under normal conditions with a normally functioning gall bladder this liver bile enters the gall bladder and is stored there. The duodenal juice recovered during the secretin test under

these normal conditions remains, therefore, entirely clear or very little bile-stained. Only toward the end of the test, when the capacity of the gall bladder is overreached, bile may be discharged, causing discoloration of the clear pancreatic juice.

In cholecystectomized individuals, or when for any reason the cystic duct is occluded, the same conditions prevail as after experimental ligation of the cystic duct: the normal cycle of bile storage no longer takes place and the entire liver bile elaborated through the stimulus of secretin is discharged into the duodenum. This causes a marked discoloration of the pancreatic juice as well as an increase in the total volume. The study of the bile pigment curve in the duodenal juices obtained during the test, as shown by Agren and Lagerlof (3), presents an important method of diagnosis in determining the status of the biliary apparatus, and helps to differentiate the normally functioning gall bladder from pathologic states where the cystic duct is occluded by stone or atresia.

It may be stated here that the secretin used in our work contains no cholecystokinins. Experiments by Agren (2) with pure secretin on the isolated gall bladder of the guinea pig showed no effect on the contraction of the gall bladder.

The present report consists of a series of forty-six cases on whom fifty-seven tests were performed. These comprise twenty-five normal cases on whom thirty-one tests were performed and seventeen cases with disease of the biliary tract on whom twenty-two tests were performed. In addition there were four cases of non-visualization of the gall bladder by X-ray, in which the secretin biliary pigment curve was normal. The pathologic material includes the following groups of cases:

- a. Non-functioning gall bladder due to closure of the cystic duct.
- b. Cholecystectomized cases.
- c. Obstruction of the common duct, benign and malignant.
- d. Toxic Hepatitis.
- e. Cholelithiasis with normally functioning gall bladder.

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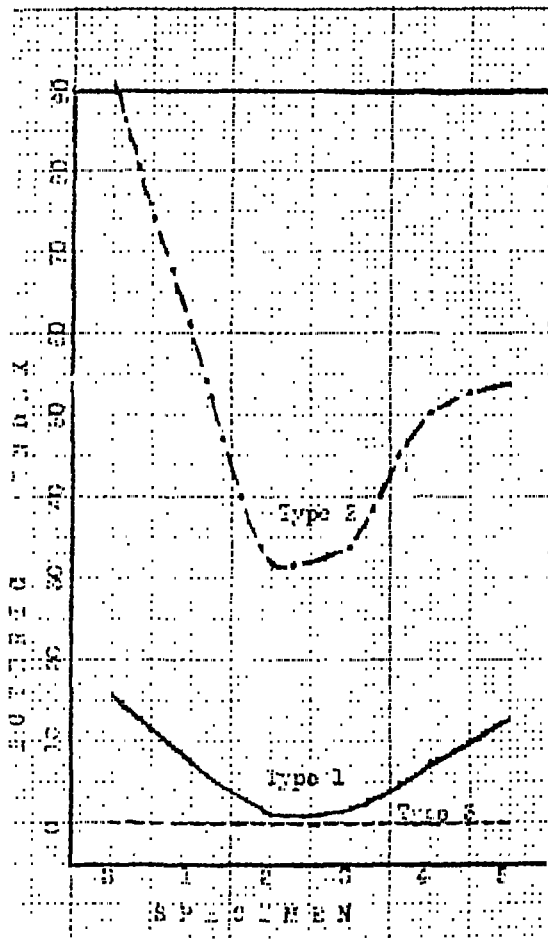


Fig. 1. Diagram of the three types of biliary pigment curves during the secretin test. Average of all tests.

The method used was to determine the icteric index of the duodenal juices before and in every sample after the injection of secretin and to study the biliary pigment curve during the 80 minute test period.

We distinguish three types of curves (Fig. 1).

#### Type I—THE NORMAL CURVE

Before the injection of secretin the duodenal juice (basal specimen) is bile stained. After the injection of secretin, with the marked increase of flow of pancreatic juice, the bile discoloration quickly thins out and within 5 to 10 minutes the duodenal juice becomes colorless. In performing the secretin test specimens are collected for two 10 minute periods and three 20 minute periods. The duodenal juice usually remains colorless throughout the second, third and fourth periods; only in the last 20 minute period may the bile discoloration reappear. During this entire time the liver bile which has been secreted enters the gall bladder and is stored there. Toward the end of the test the overfilled gall bladder may discharge some bile into the duodenum causing various degrees of discoloration. Occasionally such discharge of bile from the gall bladder may take place earlier in the test,

especially if the gall bladder was previously overfilled. Even when such an early admixture of bile has occurred there is always a period, either before or after the discharge, when the bile discoloration of the duodenal juice sinks to a very low icteric index.

In this series of normal cases (Table I) the icteric index in the basal specimen varied from zero to 86. After the injection of secretin the icteric index fell to zero in twenty-one of the twenty-five cases. In three cases it fell to 3 and in only one case it fell to 10. In seven cases the icteric index remained zero throughout all the specimens. In eight cases the index rose from 12 to 100 in the last two periods of the test. The fall in icteric index to very low levels approximating zero is the characteristic feature of the normally functioning gall bladder. Nineteen cases of the above series were subjected to X-ray study of the gall bladder with the dye. All gave normal findings with good concentration and normal emptying.

#### Type II—BILIARY PIGMENT CURVE IN THE NON-FUNCTIONING GALL BLADDER AND FOLLOWING CHOLECYSTECTOMY

In this group of cases every sample of duodenal juice recovered during the secretin test is deeply bile stained. In spite of the marked dilution due to the greatly increased flow of pancreatic juice, the duodenal fluid never becomes clear.

In addition to the increased concentration of bile pigment in this group one also notes an increased volume of duodenal juice recovered during the secretin test. This increased volume is due to the addition of the liver bile which ordinarily enters the gall bladder and is stored there. From the average increase in

TABLE I

Normal cases—indicating type I icteric index curve after secretin

Case	Specimen					
	Basal	1	2	3	4	5
R. W.	5	3	0	5	12	12
W. C.	10	8	0	0	0	5
B. W.	15	8	0	12	8	7
E. S.	8	3	0	0	0	2
M. L.	6	0	0	0	0	0
I. I.	2	0	0	0	0	0
C. B.	0	0	0	0	0	0
N. S.	0	0	0	0	0	0
S. G.	30	2	0	0	3	3
H. B.	0	0	0	7	23	4
M. B.	5	0	0	0	5	7
F. H.	5	3	0	0	0	4
D. R.	34	7	7	0	8	33
S. K.	6	4	3	0	0	0
M. H.	0	0	0	0	0	0
W. C.	10	5	5	3	9	38
D. R.	79	35	3	8	65	33
I. H.	0	0	0	0	0	0
J. R.	50	60	0	0	33	100
M. R.	0	5	0	4	4	1
M. R.	10	8	0	0	5	8
S. R.	12	8	6	0	0	8
S. F.	12	10	0	0	0	0
A. H.	43	11	1	0	0	2
J. P.	25	7	8	10	30	50
J. P.	10	7	0	1	12	19
J. P.	12	0	0	0	10	15
J. P.	30	2	0	3	6	10
S. S.	6	0	0	0	0	0
I. I.	37	19	0	0	0	0
J. L.	86	75	10	23	19	17

total volume of duodenal fluid obtained one may estimate the total output of liver bile during the period of the secretin test. Our figures indicate that for the 80 minute test period this is as high as 60 to 80 cc. This is well within the capacity of the normal gall bladder. This constant increase in concentration of bile pigment in the duodenal juice throughout the test period is of great diagnostic importance in the recognition of a diseased, totally non-functioning gall bladder with complete obstruction of the cystic duct.

In this group there were seven cases of non-functioning gall bladder (Table II) and three cholecystectomized cases (Table IIa). The former included one

TABLE II

*Cases of non-functioning gall bladder—indicating type II icteric index curve after secretin*

Case	Specimen					
	Basal	1	2	3	4	5
E. G.	50	63	30	25	27	23
F. G.	121	75	30	52	75	70
T. H.	45	32	18	17	19	16
M. M.	55	40	48	33	53	68
M. H.	93	53	23	29	34	60
G. W.	22	55	27	35	51	61

TABLE IIa

*Cholecystectomized cases—type II icteric index curve after secretin*

Case	Specimen					
	Basal	1	2	3	4	5
B. N.	125	46	24	28	51	55
T. B.	55	36	30	23	41	30
B. N.	136	100	39	50	75	115

case of spontaneous biliary fistula between the gall bladder and the first portion of the duodenum; and three cases of cholelithiasis with impacted stone in the cystic duct. All the above four cases were not visualized on X-ray study with the dye and the diagnosis in each was subsequently substantiated at operation. Of the remaining three, one was a case of clinically unmistakable gall bladder disease, one a case of cirrhosis of the liver in a diabetic with a pathologic gall bladder and the third a case of steatorrhea. In all of these the gall bladder failed to visualize on repeated X-ray examination.

In this group the icteric index of the basal specimens varied from 22 to 201 in the non-functioning gall bladder and from 55 to 136 in the cholecystectomized cases. After the injection of secretin the icteric index varied between 23 and 50 and in only one instance it dropped to 17. Thus in the second and third specimens when the dilution is greatest the icteric index remains high and does not drop below 17.

#### *Type III—BILIARY PIGMENT CURVE IN OBSTRUCTION OF THE COMMON BILE DUCT*

When the common bile duct is completely obstructed due to stone, tumor or atresia, bile cannot enter the

duodenum and the duodenal juices remain colorless throughout the test.

This group comprised three cases (Table III), the first being a benign atresia of the common duct; the second, primary carcinoma of the common duct; and the third, carcinoma of the head of the pancreas. The first two cases were confirmed at operation. The third case is an old lady, not operated upon, but in whom the clinical features were such as to leave no doubt as to the clinical diagnosis. There was a large palpable mass with X-ray findings of a pressure defect of the stomach and the secretin test showed an obstruction of the pancreatic duct. All these patients were intensely jaundiced as can be seen from the Van den Bergh figures in the table. The urobilinogen in the urine was entirely absent (4).

We have pointed out in our previous paper that the secretin test is of extreme value in this group of cases in helping to establish the origin of the jaundice. A good volume response in the secretin test points to patency of the pancreatic duct, which would tend to rule out pancreatic involvement. Although the material is too scanty for generalization at the present time the possibility must be considered of a small tumor of the pancreas so situated that it may compress the common duct and leave the pancreatic duct entirely patent.

One case of toxic hepatitis with jaundice (Van den Bergh—8.2 u) was subjected to examination with the secretin test three times over a period of three weeks, first during the height of the disease and later when the patient was considerably improved (Van den Bergh—1.4 u). In all the three examinations bile was persistently present in the duodenum and at the height of the disease the bile pigment concentration curve behaved in a similar manner as in the group with non-functioning gall bladder. Later, with improvement of the patient and return of the biliary

TABLE III

*Cases of obstruction of common bile duct—indicating type III icteric index curve after secretin*

Case	Specimen						Van den Bergh u.
	Basal	1	2	3	4	5	
G. E.	0	0	0	0	0	0	8.2
G. E.	0	0	0	0	0	0	11.8
O. K.	0	0	0	0	0	0	6.4
R. P.	0	0	0	0	0	0	11.5

apparatus to normal function the bile pigment concentration curve returned to normal.

Our series also include three cases of gall stones visualized in X-ray, each with one stone in the fundus, with normally functioning gall bladder. The icteric index curve in these cases, after secretin, was normal.

In this report we also include four cases in which X-ray study with the dye failed to visualize the gall bladder and a clinical diagnosis of pathologic gall bladder with non-function was made. The secretin test in all these cases revealed a normal behavior of the biliary pigment concentration curve of the duodenal



fluid. As can be seen from Table IV, the icteric index dropped to 3 or to zero. Subsequent X-ray examination with the dye substantiated the findings of the secretin test by revealing a normal gall bladder.

### SUMMARY AND DISCUSSION

Secretin in addition to causing an increased flow of pancreatic juice also possesses a marked choleretic effect. An intravenous injection of secretin produces an increase in flow of liver bile, estimated in our work to amount to 60 to 80 cc. during the 80 minute test period. Under normal conditions of the biliary appa-

TABLE IV

Cases of non-visualization of gall bladder by X-ray with normal icteric index curve

Case	Specimen					
	Basal	1	2	3	4	5
L. C.	60	19	3	11	27	23
G. F.	35	3	0	0	0	5
B. W.	5	0	0	0	0	0
S. Z.	11	3	0	0	0	0

ratus this secretion of liver bile enters the gall bladder and is stored there, resulting in the majority of instances in a colorless duodenal juice. When, however, the function of the gall bladder is impaired, such as by occlusion of the cystic duct or when the gall bladder has been removed, this newly secreted liver bile enters directly into the duodenum and causes a marked discoloration of the pancreatic juice.

By studying the icteric index curve of the different samples of duodenal juice obtained during the secretin test one can differentiate the normally functioning gall bladder from the diseased non-functioning gall bladder.

We recognize three types of biliary pigment curves. Type I is the normal curve where invariably the icteric index approximates zero either throughout the entire test or at least in the second or third samples collected; type II, the diseased and non-functioning gall bladder where the biliary pigment curve remains high in every sample collected and the icteric index varies between 30 and 50 but never dropping below 17 in our series; type III, in jaundiced individuals where the common duct is completely obstructed and the icteric index remains zero in all the specimens of the test. This helps to differentiate the obstructive from the non-obstructive jaundice as illustrated in the case of toxic hepatitis where an abundance of bile was present in the duodenal juice.

The test has been especially valuable in those doubtful cases where the gall bladder visualized poorly in the X-ray, or in some instances not at all. In four cases of our series where for some unknown reason X-ray failed to visualize the viscus the secretin test gave a normal biliary pigment curve. Subsequent X-ray examinations of these cases substantiated the secretin findings.

In borderline cases, where X-ray study with dye reveals poor concentration with faint visualization of the viscus, the secretin test helps to determine the degree of impairment of function of the gall bladder and helps to indicate the choice of therapy.

The test is easily performed and can be carried out as an office procedure.

*Note:* We wish to thank Dr. G. Elias and Mrs. L. Schmidt for their valuable assistance in the laboratory.

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## The Influence of the Weight of the Duodenal Tube Tip on its Entrance Time\*

By

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AFTER Hammeter (1) in 1896 and Kuhn (2) in 1898 succeeded in intubating the duodenum, the first practical duodenal tube† was described by Maurice Gross (3) and independently by Max Einhorn (4) in 1910. They introduced the principle of having a metal weight to facilitate passage to the duodenum. Einhorn (5, 6) had previously succeeded in passing a bucket to the duodenum and a catheter through the thread holding the bucket. Gross first described the maneuver of having the patient lie on his right side to facilitate passage of a weight through the pylorus.

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†It is interesting to note that although this was not strictly a duodenal tube, a rubber tube was passed through a child from mouth to anus by G. Scheltens in 1905. (*Ztschr. f. klin. Med.*, 65:505, 1908). Submitted November 2, 1939.

Modifications of these tubes, of which there are at least fifteen, consist for the most part in increasing the weight of the tip (Palefsky, 1914) (7), in substituting slots in the metal tip for perforations (Rehfuess, 1914) (8), in changing the shape of the tip to facilitate withdrawal and to eliminate the necessity for tying it (Lyon, 1920) (9), in making it still heavier and encasing it in rubber (Moses Einhorn, 1938) (10). In the meantime Jutte (1912) (11), made a small metal tip and used soft rubber which required a wire obturator. Levin (1921) (12), did away with the metal tip entirely, by using a plain rubber catheter with an eye at its terminal end which could be passed through the nose. Twiss (1933) (13) used larger tubing and a small narrow metal tip with concave

slots, attached to which by means of a swivel joint, is a solid ball which he believes acts as a leader in drawing the bucket into the duodenum and anchors it there.

The advantages claimed for various of these modifications fall into the following groups:

1. Ease of passage to the stomach.
2. Success in entering duodenum.
3. Anchorage in duodenum.
4. Avoidance of clogging by food or mucus.
5. Avoidance of injury to the mucous membrane.
6. Ease of withdrawing past the glottis.

The substitution of the wide slots for the circular holes introduced by Rehfuß, has been retained in all the subsequent metal tips. Moses Einhorn (1938) claims that by encasing the metal in rubber, the patients' fear that the tip may become detached is eliminated, the chance of injury diminished, and that the added weight favors passage to the duodenum.

The observations below were made in the course of 396 diagnostic drainages at the New York Hospital during the past three years. Four of the tubes were used—the Rehfuß, Twiss, Levin and Moses Einhorn (1938). The weights of their tips are:

- Levin tube. . . . No weighted tip  
Twiss tube. . . . 69 grains (including the leader)  
Rehfuß tube. . . 75 grains\*  
Einhorn tube. . 150 grains

The patients were not selected for the metal tipped tubes. The Levin tube, however, was used chiefly with feeble or elderly patients, or when esophageal varices were suspected. All the tubes were passed by the same trained assistant. The clinic period began at 8:30 a.m. and ended at 11:00 a.m. The technique described by Lyon (14) was followed: The tube is passed to the stomach, the stomach is washed with warm water until the return is clear, 100 cc. of warm water is introduced, the tube is clamped and the patient placed on his right side. He is instructed to swallow slowly to the duodenal mark so that it is not reached for twenty minutes by the clock. If at the end of thirty minutes no duodenal contents are obtained, the tube is withdrawn to the stomach and the process repeated. If a satisfactory drainage is not obtained the patient is fluoroscoped to determine the position of the tip.

Scores were kept on the four tubes as follows:

1. Entrance time was considered normal when the duodenum was intubated within 30 minutes.
2. Entrance time was considered delayed if the duodenum was intubated within two hours.

\*Although in the original description the weight of the Rehfuß tip is given as 90-120 grains, the tip actually used weighs 75 grains.

3. If the duodenum was not intubated within two hours the drainage was discontinued and listed as unsuccessful.

## RESULTS

396 intubations were attempted. In a two-hour period 352 or 88.9% were successful; 44 or 11.1% were unsuccessful. Table I shows the results with the four tubes.

TABLE I

Tubes	Wt. of Tips (Grains)	No. of Cases	Successful
Levin	0	45	42 91.3%
Twiss	69	143	126 88.1%
Rehfuß	75	107	98 91.6%
Einhorn	150	100	86 86.0%
Total		396	352 88.9%

There is no significant difference in the percentage of successes with any of these tubes in a two hour period. The adding of a metal tip of various weights had no advantage over a plain rubber catheter in this interval.

Does the weighted tip, however, reach the duodenum sooner, and is the weight of the tip a factor? Table II shows the intubation time divided into normal (less than 30 minutes) and delayed (within 2 hours) for only the successful drainages:

TABLE II

Successful cases—Entrance time

Tubes	Wt. of Tips (Grains)	No. of Cases	Normal	Delayed
Levin	0	42	28 66.6%	14 33.4%
Twiss	69	126	95 77.7%	31 22.3%
Rehfuß	75	98	76 77.5%	22 22.5%
Einhorn	150	86	67 77.9%	19 22.1%
Totals		352	266 75.8%	86 24.2%

This indicates that all of the weighted tips, regardless of their weight, proceed to the duodenum with equal rapidity, and that nothing was gained in this respect by increasing the weight of the Moses Einhorn tip to 150 grains. The Levin tube appears to proceed to the duodenum at a slower pace. However, we are dealing here with a selected group of patients in poorer general health, so that this point is not yet proven. Table III reviews the attempted passages of

TABLE III  
Summary of results

Tubes	Wt. of Tips (Grains)	No. of Cases	Entrance Times		
			Normal	Delayed	Unsuccessful
Levin	0	46	28 60.9%	14 30.4%	4 8.7%
Twiss	69	143	95 66.4%	31 21.7%	17 11.9%
Rehfuß	75	107	76 71.0%	22 20.6%	9 8.4%
Einhorn	150	100	67 67.0%	19 19.0%	14 14.0%
Totals		396	266 67.2%	86 21.7%	44 11.1%

all the tubes to the duodenum, successful and unsuccessful.

We are able, I believe, to state that increasing the weight of the tip beyond 69 grains (Twiss Tube) does not hasten the intubation time. It remains to be determined if a metal weight helps at all in this respect, although these figures suggest that it does.

### OTHER CLAIMS

These cannot be accurately determined, so that we are dealing merely with impressions. We believe that covering the metal tip with rubber is a desirable modification. Patients occasionally are worried by the possibility of the tip becoming detached with other tubes. A satisfactory volume of bile can be obtained with each of the tubes described—clogging has been infrequent. We believe that the greatest factor in causing trauma to the mucous membrane is suction, and it should be scrupulously avoided, except just enough to start the siphonage.

Tubes slipping out have not been a serious problem. On one occasion, during my internship, I saw a fatal hemorrhage from esophageal varices following the use of a metal tip—a blood clot was present on the tip when it was withdrawn. Although this is a very rare occurrence, its possibility should be remembered.

### CONCLUSIONS

1. A successful intubation of the duodenum was accomplished in a two-hour period with any one of four tubes used, in about 90% of the attempts.

2. A lead weighted tip appears to hasten entrance into the duodenum. This, however, has not been determined beyond doubt.

3. Increasing the weight of the tip from 69 grains (Twiss Tube) to 150 grains (Moses Einhorn Tube 1938) does not appear to accelerate its passage, or increase the percentage of successes.

*Note:* I am grateful to Elsa Nussbaumer, R.N., for her technical assistance.

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## A Method for the Continuous Recording of Gastric pH in Situ\*

### II. Experimental Details

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PREVIOUS investigators have studied gastric acidity by means of the Pavlov pouch and also by the method of frequent aspirations. Samples of the specimens obtained by these methods were then titrated against 0.1 N sodium hydroxide with phenolphthalein or Töpfer's reagents as indicators and the results were expressed in terms of free hydrochloric acid or total acid respectively.

With the advent of the glass electrode the gastric acidity has frequently been expressed in terms of pH units. In all such instances the measurements were performed on aspirated specimens. In order to obtain pH values of the gastric juice *in situ* we have devised a glass electrode for direct use in the stomach (1).

Two modifications of the bulb form of the glass electrode of the silver-silver chloride type were found to be satisfactory for this purpose. One was blown

from 2 mm. glass tubing and provided with a hard glass or rubber cylindrical jacket of 10 mm. diameter with an open end and perforated wall, to allow free circulation of the gastric contents around the glass electrode. The other was an unshielded bulb, 8-10 mm. in diameter, held away from the stomach wall by means of a small rubber balloon fixed around the neck of the electrode and inflated after introduction of the electrode into the stomach.

Employing either modification, the platinum lead of the electrode was joined to well-insulated flexible metal-sheathed multi-strand copper wire which was passed through a No. 18 fr. Levine tube, whose lower extremity was hermetically sealed to the electrode. (Diagram 1). For aspiration purposes, a second Levine tube with all openings closed with balloon rubber save that immediately opposite the electrode, was attached alongside the tube carrying the electrode and projecting 2-3 cms. to prevent contact of the electrode with the stomach wall. By means of a moist-

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ened thread passing through this aspirating tube contact was made with the reference electrode which was of the saline silver-silver chloride type. (Otherwise contact was made through the body by direct external contact of the reference electrode with the skin; it being necessary to compensate for extraneous potentials when using this method).

The leads from the stomach and reference electrodes were connected to a Beckman pH meter which in turn was connected to a recording potentiometer. The aspirating Levine tube was connected through a 3-way stopcock with a glass-ball trap and a rubber bulb which was compressed at regular intervals by a piston driven by a slowly rotating motor. (Diagram 1). This pumping system periodically withdrew and returned about 35 cc. of gastric contents and in this manner

distilled water. The pH was determined and after return to the stomach was again measured *in situ* by the continuous recording instrument. After a satisfactory control run of 5-10 minutes, 1 gram of sodium bicarbonate in 100 cc. distilled water was introduced through the Levine tube and followed by 50 cc. of distilled water. Continuous recordings were made throughout the experiment with occasional interruption for withdrawals of gastric juice for comparative external determinations.

The instillation of alkali into the stomach caused an immediate rise in pH, followed by a gradual fall until the end point (neutralization point of added alkali) was reached when an abrupt fall in pH took place. (Fig. 1).

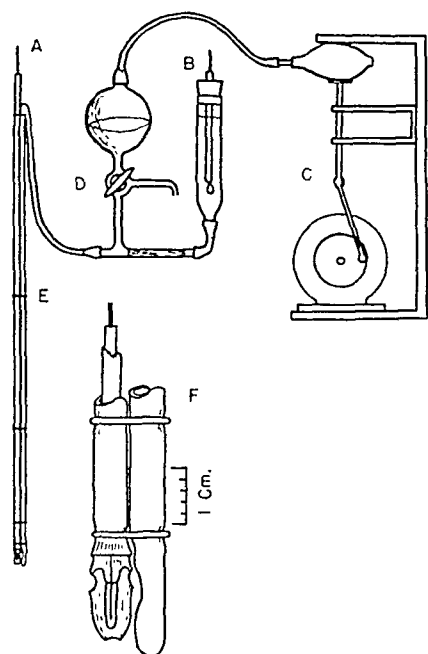


Diagram 1. Arrangement for the determination of gastric pH in situ. A—Glass electrode lead to pH meter; B—Reference electrode; C—Mechanical pump; D—Glass reservoir; E—Glass electrode and aspirating tube; F—Detail of glass electrode and aspirating tube.

continuously bathed the glass electrode with the agitated stomach fluid.

The following experiments were performed on dogs anesthetized with morphine sulfate (8 mgm. per kgm. by subcutaneous injection) and chloralose (70 mgm. per kgm. by intravenous injection). The anesthetized dog was placed in supine position at an angle of 45 degrees. The double Levine tube was introduced until it reached the greater curvature of the stomach and was then withdrawn until it was just above this depth. The actual position was determined by fluoroscopic examination.

A pH reading was made with the stomach electrode and this value was checked against the pH of an aspirated specimen measured with an external glass electrode instrument. The residual total gastric content was then aspirated, and diluted to 100 cc. with

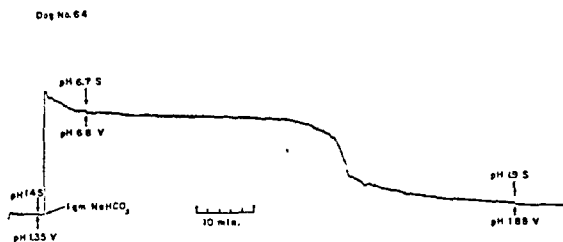


Fig. 1. Effect of 1 gm.  $\text{NaHCO}_3$  on gastric pH of a dog with hypersecretion induced by a continuous histamine injection (0.5 cc. per hour). S = pH determined from the tracing using the stomach electrode. V = pH of corresponding aspirated specimen using a standard electrode.

## DISCUSSION

This work has been carried out over a period of eighteen months. The many irregular results which were first obtained were found to be due to technical faults which were gradually eliminated. In the early experiments when no guard was used to hold the electrode away from the gastric mucosa there were marked discrepancies between the pH values given by the gastric electrode and those obtained from the aspirated specimen. The use of a guard only partially corrected these discrepancies and the results found under these conditions were similar to those recently reported by Eyerly and Breuhaus (2). As long as such variations between almost simultaneous readings persisted, we felt that the technic was still faulty. Two causes for these great differences in pH were recognized; the glass electrode was being trapped in a spastic antrum where gastric secretion poured directly onto it and where it was reached by little or none of the residual gastric content; and the diffusion in the stomach was extremely slow unless agitation was provided. Although agitation is normally absent in the stomach we believe that uniform mixing should be provided in any method of measuring the efficacy of antacids. Eyerly and Breuhaus (2) attempted such mixing by thrice passing 20 cc. of gastric content backwards and forwards before comparing their readings, but their charts seem to indicate that they did not obtain complete mixing.

We overcome the first obstacle by determining under the fluoroscope the location in the stomach of 250 cc. of barium suspension and by accurately placing the electrode in this location. The second difficulty was

surmounted by the use of the continuous pump described above and by placing the opening in the aspirating tube opposite the electrode. With these modifications, the readings obtained within the stomach checked with those of the aspirated specimens within 0.5 pH units. (Fig. 1). The constantly changing gastric secretion and absence of complete mixing makes it impossible to consistently reduce the discrepancy below this figure.

As the alkali is instilled through the Levine tube the peak (a) of the rise is conditioned by the pH of the antacid solution or suspension; the immediately following plateau (b) indicates the pH of the mixture of gastric fluid and added alkali; and the duration of the gently sloping portion of the curve is a measure of the amount of alkali present and the rate of acid secretion. Variation in amount of emptying that takes place can be estimated by measuring the gastric contents at the end of the experiment.

By controlling combinations of these variables interesting data on gastric acid secretion and efficacy of antacids may be obtained.

### SUMMARY

A method for continuous recording of gastric acidity is described which consists in the introduction into the stomach of the dog of a glass electrode connected with a pH meter and a recording potentiometer. Adequate mixing of the gastric contents is accomplished by the use of an automatic aspirating and injecting device. This method is suggested as a means of studying the effect of drugs and food in normal animals and those in an induced hypersecretory state. Its clinical applications will be reported later.

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## Editorials

### SHOULD THIS JOURNAL BE PUBLISHED IN MICROFILM?

IT is almost certain that before long many scientific journals will be putting out what is called a microfilm edition. Each page of the large edition will be photographed on standard 35 mm. film and this will be read with the help of a magnifying apparatus or lectern. Such apparatus has already been devised and most libraries of any size will soon have one.

Today when the historian wishes to write a book, he usually gets all the important books, articles and manuscripts he needs copied on microfilm. This work can now be done in the larger libraries of the world for perhaps a cent a page.

In many libraries the demands for space will make it necessary that many files of old and little used journals be copied on film and kept only in this form.

Mr. Alexander S. Dowling of 134 East First Street, Corning, New York, has suggested that if enough subscribers of this Journal would care to have a microfilm edition, he would be able to make the copies at a low page rate. If enough readers are interested, arrangements can be made to prepare such an edition and to mail it each month.

W. C. A.

### DIFFERENCES IN SENSITIVENESS OF PATIENTS WITH ULCER

SINCE publishing an editorial on differences in sensitiveness of patients with ulcer, we have received a letter from Dr. G. S. de Paula e Silva of Bello Horizonte, Brazil. He states that he has now subjected over 2,000 patients to Libman's test for sensitiveness. This consists of applying pressure over the styloid process below the ear. The doctor was unable to find any marked difference in the complaints of patients in the two groups of hypersensitive and hyposensitive. He found silent duodenal ulcers occasionally in patients who appeared to be hypersensitive, and many of the hyposensitives complained of pain. He was impressed with the fact that tender abdominal points appeared more frequently in the hypersensitive than in the hyposensitive patients.

In 1937 in "Brasil-Medico" Dr. de Paula published a summary of his findings in 100 cases of duodenal ulcer subjected to Libman's test. Twenty-six per cent were hyposensitive and 74 per cent were hypersensitive. Most of the patients with duodenal ulcer were of a nervous temperament and were living under considerable strain. Some years ago Crohn showed that, as one would expect, patients with ulcer are more sensitive to the Libman test when they are having hunger pain than when they are enjoying a period of remission of symptoms.

W. C. A.

### REVIEWS OF SOME GASTRO-ENTEROLOGIC LITERATURE FOR 1939

ALL readers of this Journal will enjoy, if they have not yet read it, the splendid review of gastro-enterologic literature prepared by Chester Jones and published in the October, 1939 number of the "Archives of Internal Medicine." The most interesting advances seem to be those made in the field of research as to the causes and treatment of ulcer. Very encouraging has been the discovery that substances in the urine will lower acidity and relieve the symptoms of ulcer. There is great activity today in the field of gastroscopy, where much is being learned about the several types of gastritis.

Another article that all gastro-enterologists will want to read is the excellent review of regional ileitis prepared by Robert Shapiro and published in the August, 1939 number of the "American Journal of the Medical Sciences." There is a large bibliography appended.

Another excellent review of the year's literature on the diseases of the liver and biliary tract was published by Carl H. Greene and Richard Hotz in the Archives of Internal Medicine for April, 1939.

Gastro-enterologists will find much to interest them also in the review of neuropsychiatry prepared by Stanley Cobb and published in the Archives of Internal Medicine for December, 1939.

W. C. A.

# I. Fecal Residue of Fat, Protein and Carbohydrate in the Normal Dog\*

By

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**B**EFORE beginning a study of the influence of the pancreatic juices and bile on intestinal digestion and absorption, it was necessary to determine accurately the capacity of the normal dog to utilize various amounts of fats, protein and carbohydrate. It was necessary also to look for possible influences of one foodstuff upon the utilization of another.

According to most reports, normal dogs utilize from 90 to 98 per cent of ingested fat. Voit found that the fat loss in the feces was from 4 to 11 per cent, and up to certain limits, the utilization increased directly with the amount of ingested fat. Similarly Cruickshank reported a fat loss of 2 per cent with a fat-rich diet, and a 13 per cent loss with a fat-poor diet. It was pointed out by Schmidt and Strasburger that much of the fecal fat is of metabolic origin. Müller found that this "metabolic fat" in fasting dogs, amounted to from 0.18 to 2.3 gm. daily. Evidently the efficiency of fat utilization is lessened when the amount of fat in the food is much restricted.

According to Arnschink, the digestibility of different fats depends on their melting point. In his experiments only from 9 to 14 per cent of stearin, the melting point of which is 60° C., was utilized, while lard, which has a melting point of 34° C., was almost completely absorbed. Munk and Rosenheim showed that protein restriction in the diet for from six to eight weeks resulted in decreased utilization of fat, but this was not confirmed by Jägerroos.

All investigators agree that most of the fecal fat in normal dogs is in the split form. Müller stated that 67 per cent was composed of fatty acids and soap, while Pratt, Lamson and Marks found that it consisted of 46 per cent neutral fat, 40.5 per cent fatty acid, and 13.5 per cent soap.

The utilization of protein, as estimated by the residue of nitrogen in the feces, in normal dogs has been usually found to be 90 to 95 per cent under normal dietary conditions. The work of Voit, in which the contents of closed intestinal loops were found to contain as much nitrogen as is found in the feces, indicated that the fecal nitrogen is principally of metabolic origin. Mosenthal estimated that the succus entericus contains three or four times more nitrogen than the feces, and he expressed the opinion that reabsorption of the nitrogen prevented a greater loss. MacNeal, Latzer and Kerr stated that the bacterial nitrogen constitutes 46 per cent of the total fecal nitrogen. The experiments of Magnus-Levy and of

Rubner showed that the efficiency of protein utilization is directly proportional to the intake, and furthermore, that an increase in the residue content of the food is attended by a proportionate loss of fecal nitrogen. Atwater and Longworthy reported the coefficients of digestibility of nitrogen to be 98 in animal food, 85 in cereals and 80 in vegetables and fruit.

The utilization of carbohydrate is dependent on the digestibility of the food. To illustrate this, Rubner cited an experiment in which a dog excreted 5.8 gm. of carbohydrate daily in the feces on a diet containing 529 gm. of fine wheat flour, and the same dog excreted 37.2 gm. daily on a diet containing 504 gm. of coarse grain. Most investigators have found carbohydrate utilization to be 95 to 98 per cent on a mixed diet, although Beazell, Schmidt and Ivy were unable to detect any fecal carbohydrate after feeding a diet of 62 per cent starch. It is generally agreed that fecal carbohydrate is derived from the diet, and is not of metabolic origin.

## METHODS OF INVESTIGATION

The utilization of each foodstuff was determined by conducting metabolic experiments of five days' duration, during which time the fecal excretion was determined.

Four different diets were used. The standard diet consisted of 39.5 per cent horse meat, 37 per cent cracker meal, 6.6 per cent lard, 3.3 per cent bone ash, and 13.6 per cent canned tomatoes. The high carbohydrate diet was composed of equal parts of cracker meal and standard diet. Both the standard diet and the carbohydrate diet were fed once each day in an amount of 24 gm. for each kilogram of body weight. The high protein diet consisted of 20 gm. of horse meat and 4 gm. of standard diet per kilogram of body weight, while the high fat diet was made up of 10 gm. of lard and 4 gm. of standard diet per kilogram of body weight.

Powdered carbon and barium sulfate were used as alternate markers, and the stools were collected daily. The entire specimen was well triturated, and an aqueous emulsion of a representative sample was prepared. Estimations of fat, protein and carbohydrate content of this emulsion were secured.

The Fowweather modification of the Saxon method of fat analysis was used. The total fat, neutral fat and free fatty acid content were determined.

The total nitrogen content was determined by the method of Kjeldahl. It was found that the preliminary addition of 10 cc. of concentrated sulfuric acid to the weighed sample for a period of twelve hours greatly reduced the usually prolonged time of actual digestion.

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‡Abridgement of thesis submitted by Dr. Coffey to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Ph.D. in surgery.

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The Schaeffer-Hartman method of sugar analysis was employed after acid hydrolysis of the total carbohydrate.

The proportion of dry solids in the feces was determined in each experiment by drying a weighed sample.

### RESULTS OF INVESTIGATION

The average figures for the recovery of the fat, nitrogen and carbohydrate in the feces of five day

TABLE I  
*Fecal excretion of fat by normal dogs\**

Diet	Number of Experiments	Daily Fat Intake, gm.	Fecal Fat, Per Cent of Intake	Per Cent of Fecal Fat Present as		
				Neutral Fat	Fatty Acids	Soaps
Fat	22	113	3.59	14.8	42.6	42.6
Standard	14	35	2.11	38.8	49.4	11.8
Carbohydrate	13	33	2.97	37.0	59.6	3.4
Protein	11	17	3.99	34.6	54.0	11.4

\*All figures given represent averages calculated from the series of experiments indicated.

periods are given in Tables I, II and III. In no instance did the fecal excretion of any of the substances exceed by more than a third the average values given, so that the individual variations are without physiologic significance.

The fat diet used in these experiments when fed for a period of six to eight weeks produced fatty livers with a fat content of about 20 per cent. Our idea was to exhaust the capacity of the dog to utilize fat, and thus to increase the amount excreted in the feces. Actually it did not. In two animals which were fed the fat diet for fifty-five consecutive days the fecal excretion of fat remained within normal limits. The ratio of neutral to hydrolyzed fat, however, increased appreciably toward the end of the experiment.

### COMMENT

Within wide limits the utilization of foodstuffs by normal dogs proved to be highly efficient.

TABLE II  
*Fecal excretion of nitrogen by normal dogs*

Diet	Protein Intake, gm.	Fecal Nitrogen, Per Cent of Intake	Fecal Nitrogen, gm.	Fecal Dry Solids, Per Cent
Fat	5.2	47.4	0.36	56.1
Standard	33.2	12.2	0.66	63.9
Carbohydrate	32.0	15.9	0.80	49.6
Protein	50.0	5.2	0.11	61.2

The percentage of fat loss in the feces was little influenced by the amount of fat in the diet, varying from 2.11 per cent to 3.99 per cent (Table I). This was preponderantly fatty acids when small or moderate amounts of fat were fed, only 34 to 38 per cent of the fecal fat being neutral. On feeding the high fat diet, only 14.8 per cent was neutral fat. Soap was present

in only small amounts, except when the high fat diet was used, when it averaged 42.6 per cent of the fecal fat.

The fecal excretion of nitrogen, on the contrary, was markedly influenced by variations in the diet. This loss varied inversely with the protein intake, representing 5.2 per cent in experiments using the high protein diet, and 47.4 per cent when the high fat, low protein diet was fed. However, a consideration of the nitrogen excretion in absolute amounts revealed a direct relation between the protein excretion in grams and the non-nitrogenous roughage contained in the diet. In the calculation of fecal protein the total amount of nitrogen has been considered as protein and no attempt made to eliminate the nitrogen of non-protein sources from the calculation. It was obvious that the amount of nonprotein nitrogen increased with the bulk and water content of the feces. The similarity of the total nitrogen content of the feces of animals receiving the protein-rich and the protein-poor diets would indicate that the amount of fecal nitrogen was but slightly influenced by the protein content of the

TABLE III  
*Fecal excretion of carbohydrate by normal dogs*

Diet	Carbohydrate Intake, gm.	Fecal Carbohydrate, Per Cent of Intake	Fecal Carbohydrate, gm.
Fat	12.1	3.02	0.36
Standard	78.6	1.38	1.08
Carbohydrate	147.2	1.04	1.54
Protein	12.7	2.50	0.32

diet. An average excretion equivalent to 25.2 gm. protein occurred on feeding the high carbohydrate diet which contained much roughage, while only 12.9 gm. was lost when the high protein diet was used (Table II). These findings are convincing evidence in favor of the metabolic origin of the nitrogen in the feces.

The utilization of carbohydrate was only slightly influenced by the amount in the diet. There was a small loss of carbohydrate with all diets used, and this loss increased with the carbohydrate content of the diet. However it was not exactly proportional to it.

### CONCLUSIONS

The utilization of foodstuffs by normal dogs was found to be highly efficient. The fecal excretion of fat varied from 2.11 per cent to 3.99 per cent, most of which was fatty acids. The fecal nitrogen was found to be fairly constant in absolute amount except for a variation roughly proportional to the bulk of the feces. When calculated as percentage of the protein of the diets used, the nitrogen of the feces increased in percentage as the amount of protein of the diet decreased. With diets low in protein as much as 50 per cent of the nitrogen intake may be excreted in the feces. Carbohydrate excretion in the feces was only slightly affected by diet, varying from 1.0 per cent to 3.0 per cent.

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## II. The Effect of the Exclusion of Bile on the Absorption of Foodstuffs\*

By

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and

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THE role of bile in the utilization of fat has long been the subject of experimental investigation, and the importance of this secretion as compared to that of the pancreatic juice in the digestion and absorption of fat and other foodstuffs was determined in this study.

As the result of experimental and clinical studies, Müller in 1887 found that the exclusion of bile from the intestinal tract was accompanied by the loss in the feces of from 52 to 78 per cent of the ingested fat. The utilization of protein and carbohydrate was not appreciably affected. Munk occluded the common bile duct in a dog, and a fecal fat loss of 44 per cent of

26 per cent fat loss. Most observers agree that after the exclusion of bile there is no evidence of defective lipolysis in the excreted fat.

It has been suggested that the exclusion of bile from the duodenum results in defective fat utilization because of the absence of the biliary secretagogue influence on the pancreas. However, Ivy, and Dragstedt and Woodbury, have demonstrated that the response of the pancreas to food is not affected by the absence of bile.

### METHODS OF INVESTIGATION

A male dog weighing 12.5 kg. was operated on and the common bile duct was ligated and divided 2 cm.

TABLE I  
Fecal excretion following ligation of the common bile duct\*

Diet	Daily Intake of Fat, gm.	Fecal Fat, % of Intake	Per Cent of Fat Present as			Nitrogen, % of Intake	Carbohydrate, % of Intake
			Neutral	Fatty Acids	Soaps		
Fat	108.0	47.2	48.8	32.8	18.4	182.0	4.8
Standard	19.2	47.2	29.0	46.0	25.0	20.7	1.2
Protein	10.0	27.8	62.2	37.8	0.0	9.6	3.1

\*All figures given represent averages calculated from the entire series of experiments.

the dietary fat resulted. Hédon and Ville established biliary fistulas in dogs, and they reported the utilization of 69 per cent of milk fat and of 45 per cent of olive oil. Metabolic studies of fat utilization in clinical cases of obstructive jaundice have been conspicuous by a lack of agreement, probably attributable to varying grades of obstruction to the flow of bile. Brugsch found that 45 per cent of the ingested fat appeared in the feces, while Schmidt and Strasburger estimated a

proximal to its entrance into the duodenum. Jaundice rapidly ensued, and metabolic studies were begun on the third postoperative day.

Five day experiments were conducted, using the high protein, high fat and standard diets, as previously described (2). The metabolic and analytic technics were identical to those employed in former studies.

The animal died six weeks after operation with a perforated duodenal ulcer.

The amounts of fat, carbohydrate and nitrogen of the feces for five day periods are given in Table I.

\*Abridgment of thesis submitted by Dr. Coffey to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Ph.D. in Surgery.  
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## COMMENT

In these experiments, the exclusion of bile from the intestine permitted the utilization of 52.8 per cent of large and moderate amounts of ingested fat. The feeding of a low fat, high protein diet was accompanied by the utilization of 72.2 per cent of fat. Only with the fat-poor diet was there a preponderance of neutral fat in the feces. The excreted fat in all experiments was solid at room temperature.

Nitrogen excretion in the feces was definitely increased when the bile was excluded from the bowel. The recovery in the feces of 182 per cent as much as was contained in the high fat diet is striking evidence

of a loss of nitrogen from the intestinal canal. The loss of nitrogen appeared to be proportional to the bulk of the feces and was independent of the protein content of the diet.

Carbohydrate utilization was unaffected by the absence of bile in the intestine.

## SUMMARY

When bile was excluded from the intestine of a dog there was a definite diminution of the absorption of fat. Carbohydrate utilization was not impaired. There was an increased loss of nitrogen which was independent of the amount of protein in the diet, but proportional to the bulk of the feces.

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### III. The Influence of the Pancreas on the Utilization of Foodstuffs\*

By

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THIS experimental study was undertaken in an attempt to determine the influence of the pancreatic juice on the utilization of fat, protein and carbohydrate. From a cursory review of the chapters on the pancreas in standard textbooks of physiology, one is led to believe that all the questions in this field have been answered but a perusal of the literature shows that many problems remain unsolved.

With his brilliant researches, Claude Bernard in 1856 was the first to focus attention on the importance of pancreatic juice in the digesting and absorption of food. He concluded that, as the result of exclusion of pancreatic juice, the foodstuffs, and especially fat, escaped digestion and absorption. Bernard's work was based principally on the observation that the intestinal lacteals contained no fat when the pancreatic juice was excluded. Contemporary investigations, including those of Herbst, Weinmann, Frerichs, and Schiff, failed to substantiate Bernard's conclusions.

Abelmann, in 1890, conducted accurate metabolic studies of digestion and absorption in experimentally produced pancreatic deficiency. He determined both the dietary intake and the fecal excretion of the various foodstuffs in dogs. After total extirpation of the pancreas, he found that none of the nonemulsified fat, but as much as half of emulsified milk fat, was absorbed. The protein absorption averaged 44 per

cent, and carbohydrate utilization was least affected. Then this same worker partially removed the pancreas and tied and divided the pancreatic ducts. Animals so treated exhibited a strikingly better utilization of fat, protein and carbohydrate than did the totally depancreatized animals.

Sandmeyer, in 1895, duplicated Abelmann's studies in partially depancreatized dogs. In 1898 Rosenberg found that ligation and division of the pancreatic ducts failed to influence the utilization of food in dogs, although subsequent extirpation of the atrophic remnant of pancreas was followed by a severe loss of fat, protein and carbohydrate in the feces.

These investigators interpreted the dissimilar utilization of the foodstuffs in totally depancreatized dogs and in those in which the pancreatic ducts had been ligated as being due to the effect of the pancreatic enzymes that reached the intestine via the blood stream. In 1904, Lombroso (15, 16, 17) suggested that the pancreas elaborates an internal secretion which in combination with the external secretion governs the utilization of food. This hypothesis was based on his experiments which showed that a viable subcutaneous graft of pancreas was able to maintain food assimilation quite satisfactorily, that removal of the graft resulted in a marked fecal loss of the ingested food, and that the diversion of pancreatic juice through a fistula did not seriously injure the utilization of food. His studies indicated that this hypothetical internal secretion had its most pronounced effect on fat, a lesser one on carbohydrate, and a yet

\*Abridgment of thesis submitted by Dr. Coffey to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Ph.D. in Surgery.

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smaller one on protein absorption. In addition, he (18) found no evidence of a compensatory increase of the enzymic activity of the succus entericus, a fact militating against the hypothesis that the enzymes of the obstructed pancreatic juice reach the intestine through the blood stream.

During the ensuing five years, numerous studies, including those of Zunz and Mayer, Brugsch, Niemann, Fleckseder, and Jansen, substantiated in whole or part the findings of Lombroso. However, Sinn and Hess and Burkhardt failed to find evidence of an internal secretion controlling the utilization of food. Moreover, Visentini separated the pancreas and duodenum and found that a 60 to 90 per cent loss of fecal fat resulted. Labbé and Labbé reported a similar loss following duct ligation and partial pancreatectomy.

American investigators soon became interested in this unsettled controversy, and in 1909, Pratt, Lamson and Marks found that normal fecal excretion by dogs whose pancreatic ducts had been ligated and divided was the result of re-establishment of the continuity of the duct system. They interposed omentum between the separated pancreas and duodenum, and found that this was followed by a severe fat and protein loss. McClure, Vincent and Pratt observed that the utilization of fat and protein was improved when dogs with a pancreatic fistula were allowed to lick up the secretion. Nothmann and Wendt attributed great importance to the rapid emptying time of the stomach as a factor in deficient absorption following duct ligation and pancreatectomy.

More recent investigations have done little to clarify the problem. In Rosenblum and Krakower's studies, about half of the fat and protein and 80 per cent of the carbohydrate were assimilated by dogs with divided pancreatic ducts. Selle and Moody found unusually efficient food utilization after total pancreatectomy in dogs.

Almost all investigators agree that after total pancreatectomy or any operative procedure that keeps pancreatic juice out of the duodenum, most of the fecal fat is still split (which is hard to understand if the pancreatic juice is all-important in lipolysis). Garrod tried to explain this with the old hypothesis of a dual internal and external secretory control of fat utilization by the pancreas, the former governing absorption and the latter controlling cleavage of the fat. He assumed that in the absence of the pancreatic juice, a compensatory lipolytic activity of the succus entericus develops, but the absorption of the fatty acid can occur only if the internal secretion is being formed.

A study of the literature shows two things, one the general agreement that the total extirpation of the pancreas results in a severe loss of the foodstuffs, especially fat, in the feces, the other that dispute remains as to whether the loss of the pancreatic juice causes a comparable failure of absorption. Those who believe it does contend that the failure of such fecal excretion can be explained in two ways: (1) that the operation has failed to divide accessory ducts, and (2) that continuity of the duct has been restored through the formation of a sinus. Bernard, in his original studies of the pancreatic duct system in the dog, described a major and a minor duct. Senn found only

two ducts in his studies, as did Revell. However, Hess, in 1907, studied the pancreatic ducts in dogs by injecting into the major duct a radiopaque solution, following which a radiogram was made. He stated that usually there exist three, and often four, pancreatic ducts. Visentini completed a similar study, using a radiopaque solution, and could demonstrate only two ducts. That the pancreatic ducts can re-establish their continuity by fistula formation is attested by the observations of Visentini and of Pratt, Lamson and Marks. These latter investigators completely separated the pancreas from the duodenum, and interposed omentum in order to prevent re-establishment of continuity. However, their operation has been objected to on the grounds that the blood supply of the gland is destroyed.

The correlation of the blood fat level and the fecal excretion of fat has received relatively slight attention in experimental pancreatic deficiency. Moncrieff and Payne reported high fat levels in celiac disease, and interpreted this as indicating poor utilization rather than poor absorption of fat. On the other hand, Thyssen has observed subnormal postprandial elevations of blood fat in cases of chronic idiopathic steatorrhea. Chaikoff and Kaplan found that after total pancreatectomy in dogs the blood fat level was lowered, and by the administration of raw pancreas they were able to correct this.

## METHODS OF INVESTIGATION

Fecal excretion of the foodstuffs was determined in normal dogs following which experimental pancreatic deficiency was established by various methods. Metabolism experiments were then conducted, employing the same technic, same diets and same methods of chemical analysis as described in a previous publication (6).

The animals were fasted twenty-four hours pre-operatively, and intratracheal ether anesthesia was used in all cases. Three different surgical procedures were employed in an attempt to exclude the pancreatic juice from the duodenum. Evulsion of the pancreatic ducts, according to the technic of Mann, was selected in order to obviate the danger of re-establishment of the ducts and of interference with the blood supply to the pancreas. The minor and major ducts were isolated, divided and forcibly torn from the substance of the gland. Total pancreatectomy was carried out by blunt dissection with an aneurysm needle. Pancreatic fistulas were established by using the Elman-McCoughan modification of the Rous-McMaster technic, which consisted of evulsion of the minor duct and cannulation of the major duct. High jejunal fistulas were performed on several dogs, using the technic of Mann and Bollman.

## RESULTS

*Food utilization after evulsion of the pancreatic ducts.* The feces became bulky immediately after evulsion of the duct, and a progressive weight loss was observed in all except one animal. Death came usually in from two to four months as the result of inanition. The high protein diet appeared to exert the most favorable influence on the animal's well-being, while the high fat diet was poorly tolerated.

The amounts of fat, nitrogen and carbohydrate lost

TABLE I

*Fecal excretion of dogs after evulsion of the pancreatic ducts\**

Diet	Number of Experiments	Daily Fat Intake, gm.	Fecal Fat, Per Cent of Intake	Per Cent of Fecal Fat Present as		
				Neutral Fat	Fatty Acids	Soaps
Fat	10	106.3	47.3	65.3	25.6	9.1
Standard	11	36.0	51.2	36.3	61.5	2.2
Carbohydrate	5	36.3	65.3	31.0	56.5	12.5
Protein	6	16.7	78.6	32.2	49.6	18.2
		Protein Intake, gm.	Fecal Nitrogen, Per Cent of Intake			Fecal Nitrogen, gm.
			Average	Low	High	
Fat	10	4.8	275.0	207.0	488.0	2.08
Standard	12	34.3	64.1	41.2	91.5	3.46
Carbohydrate	5	31.8	89.3	78.5	106.5	4.88
Protein	11	50.8	29.0	15.1	45.5	2.40
		Carbohydrate Intake, gm.	Fecal Carbohydrate, Per Cent of Intake			Fecal Carbohydrate, gm.
			Average	Low	High	
Fat	10	10.16	14.7	8.1	34.7	1.48
Standard	10	81.66	26.4	8.9	50.2	21.54
Carbohydrate	5	160.2	35.4	22.9	48.8	56.60
Protein	11	15.06	7.6	3.8	19.8	1.12

\*All figures given represent averages calculated from the series of experiments indicated.

in the feces, shown in Table I, are averages of figures from several experiments of five days' duration. Only figures from feeding experiments beginning later than two weeks postoperatively are included in the table. In those experiments conducted earlier it was found that the fecal loss of fat never exceeded 20 per cent of the fat in the diet and the fecal excretion of nitrogen and carbohydrate was similar to that found in normal dogs. Between the second and fourth postoperative weeks the amount lost in the feces rapidly increased and remained fairly constant after that time. When the fat diet was used repeatedly there was some evidence of a gradually increasing loss of fecal fat as long as the experiments were continued. In numerous experiments where a large amount of the ingested fat was recovered in the feces, it appeared as an oil at room temperature, whereas the dietary fat in the form of lard was solid at a similar temperature.

An unusual sequence of events occurred in one animal after evulsion of the pancreatic ducts. Excretion of fecal fat, nitrogen and carbohydrate was increased to the expected level in four experiments begun after the twenty-second postoperative day. About seven weeks after operation the animal's general condition began to improve and in the next three weeks it regained its preoperative weight. An improvement in the utilization of food resulted in a marked diminution of fecal excretion, the amounts found in the feces ten weeks after operation being within normal limits. A second laparotomy was per-

formed thirteen weeks after the first operation, at which time the pancreas appeared as a thin fibrous cord with the exception of a small nodule of apparently healthy gland adjacent to the duodenum and attached to it by a fine filament which was probably a duct. The nodule was excised and found to weigh 425 mg., approximately one-fortieth of a normal gland. On histologic study it was found to be composed of normal acinar pancreatic tissue. Metabolic studies commenced on the second day after the second operation showed that the utilization of fat, nitrogen and carbohydrate was immediately diminished as much as would be expected several weeks subsequent to complete evulsion of the pancreatic ducts. The animal lost weight rapidly and died four weeks later. It appears from this experiment that a small portion of the pancreas is sufficient to supply all the pancreatic enzymes necessary for normal digestion and absorption of food.

*Food utilization after total pancreatectomy.* Following the total removal of the pancreas, the blood sugar concentration was maintained at 0.1 to 0.2 per cent by the daily administration of 5 to 15 units of insulin. Feeding experiments begun the second day after operation indicated an immediate loss of utilization of fats and carbohydrates. The average values found are given in Table II.

*Food utilization with complete pancreatic fistulas.* With complete pancreatic fistula, the dogs excreted more than 150 cc. of pancreatic juice each day and lost weight rapidly. Feeding experiments begun the second postoperative day indicated an immediate loss

TABLE II

*Fecal excretion after total pancreatectomy*

Diet	Number of Experiments	Daily Fat Intake, gm.	Fecal Fat, Per Cent of Intake	Per Cent of Fecal Fat Present as		
				Neutral Fat	Fatty Acids	Soaps
Fat	3	100.0	76.2	78.0	17.7	4.3
Standard	2	34.8	57.6	45.3	50.0	4.7
Carbohydrate	2	25.2	67.4	42.0	51.5	6.5
Protein	3	10.5	51.5	25.5	63.6	10.9
		Protein Intake, gm.	Fecal Nitrogen, Per Cent of Intake			Fecal Nitrogen, gm.
			Average	Low	High	
Fat	3	4.42	317	273.0	341.0	2.24
Standard	2	34.8	57.3	57.2	57.5	2.70
Carbohydrate	2	21.4	96.0	92.1	99.5	3.72
Protein	4	33.0	21.9	13.1	30.4	1.14
		Carbohydrate Intake, gm.	Fecal Carbohydrate, Per Cent of Intake			Fecal Carbohydrate, gm.
			Average	Low	High	
Fat	3	9.56	21.0	16.4	32.2	2.00
Standard	2	78.0	11.7	5.5	17.8	9.14
Carbohydrate	2	112.4	43.6	41.9	45.3	48.86
Protein	3	7.8	3.9	2.7	5.5	0.3

of utilization of fat and carbohydrate as shown in Table III. Oral administration of a few cubic centimeters of pancreatic juice prolonged the life of the animals but had no effect of increasing the utilization of food.

*Food utilization with incomplete pancreatic fistulas.* The daily excretion of pancreatic juice in these experiments ranged from 50 to 150 cc. and the animals remained in good condition without loss of body weight. The average loss of food in the feces during various five-day periods was but slightly greater than that found in normal animals (Table IV). Animals with nonfunctioning fistulas showed no deviation from normal.

*Neutral fat of the plasma.* The neutral fat content of the blood was determined at intervals of 3, 6, 9, 12, 15 and 24 hours after giving a fat meal. With this diet the level of fat in the blood of normal dogs remained fairly uniform throughout the day (8). In dogs with evulsed pancreatic ducts or complete pancreatic fistula the neutral fat in the blood remained at extremely low levels as shown in Table V. At times, after feeding, however, these animals did show some small irregular increases in the fat of their blood. We found no such changes in the blood of fasting animals. These data therefore indicate that some fat from the intestine may reach the blood, but that in the absence of secretion from the pancreas, the amount of fat absorbed is small. The addition of raw pancreas to the diet of the dogs surgically deprived of their own pancreatic juice was the only measure which consistently increased the fat content of the blood.

TABLE III

*Fecal excretion of dogs with complete pancreatic fistulas\**

Diet	Number of Experiments	Daily Fat Intake, gm.	Fecal Fat, Per Cent of Intake	Per Cent of Fecal Fat Present as		
				Neutral Fat	Fatty Acids	Soaps
Fat	2	204.8	37.6	36.9	55.6	6.5
Standard	1	49.0	50.6	14.2	73.0	12.8
Carbohydrate	1	47.0	56.0	26.4	45.4	28.2
		Protein Intake, gm.	Fecal Nitrogen, Per Cent of Intake		Fecal Nitrogen, gm.	
Fat	2	9.4	160.3		2.40	
Standard	1	46.4	104.5		7.62	
Carbohydrate	1	45.6	102.5		7.46	
		Carbohydrate Intake, gm.	Fecal Carbohydrate, Per Cent of Intake		Fecal Carbohydrate, gm.	
Fat	2	19.6	5.9		1.14	
Standard	1	110.0	13.2		14.50	
Carbohydrate	1	209.0	27.4		57.2	

TABLE IV

*Fecal excretion of dogs with incomplete pancreatic fistulas*

Diet	Number of Experiments	Daily Fat Intake, gm.	Fecal Fat, Per Cent of Intake	Per Cent of Fecal Fat Present as		
				Neutral Fat	Fatty Acids	Soaps
Fat	5	209.0	6.7	11.8	46.5	41.7
Standard	4	50.9	5.2	32.6	60.9	6.5
Carbohydrate	2	47.8	8.6	27.4	72.6	0
Protein	3	28.8	8.0	23.4	56.1	20.5
		Protein Intake, gm.	Fecal Nitrogen, Per Cent of Intake		Fecal Nitrogen, gm.	
Fat	5	9.06	71.5		1.04	
Standard	4	51.80	21.6		1.80	
Carbohydrate	2	45.80	21.1		1.72	
Protein	3	98.80	8.5		1.31	
		Carbohydrate Intake, gm.	Fecal Carbohydrate, Per Cent of Intake		Fecal Carbohydrate, gm.	
Fat	5	21.4	2.0		0.42	
Standard	4	110.6	2.4		2.74	
Carbohydrate	2	212.8	2.4		5.12	
Protein	3	19.0	3.7		0.70	

## COMMENT

As the review of the experimental work on the exocrine function of the pancreas has indicated, great controversy revolves about the question of whether the utilization of food depends on the secretion of pancreatic juice into the intestine, as was originally held by Claude Bernard and reaffirmed by most modern investigators. Lombroso (15), denying this, advanced the hypothesis that an internal secretion of the pancreas controls the utilization of food, especially fat.

After evulsion of the pancreatic ducts, most of the dogs exhibited remarkably efficient utilization of food for a variable length of time. The maximal fecal loss of fat was not attained until two to eight weeks post-operatively. Following total pancreatectomy, the fecal loss of the foodstuffs was immediately comparable to that finally developed by the dogs with evulsed pancreatic ducts. However, the maximal excretion of fat came immediately after removal of the pancreas in contrast to the gradual increase in fecal excretion observed after evulsion of the ducts. Pancreatic fistulas with loss of all secretion, were associated with a loss of foodstuffs similar to that found in the animals following pancreatectomy. The existence of an incomplete pancreatic fistula caused only slight impairment in the dog's ability to utilize food.

The persistence of the efficient utilization of food for a period after evulsion of the pancreatic ducts contrasted markedly with the immediate loss of the function following pancreatectomy or the production

of a complete pancreatic fistula. The gradual increase in the fecal loss of fat and carbohydrate in dogs with evulsed ducts was found to be strikingly paralleled by a progressive atrophy of the acinar elements of the pancreatic remnant. Histologic examination of pancreatic remnants obtained from various animals of this series indicated that much of the acinar tissue was degenerate within two weeks so that only about a tenth of the remaining acini at that time stained as normal tissue. During the next few weeks there appeared a gradual increase in the amount of connective tissue and of insular groups with a diminution of the number of recognizable acini. After from six to ten weeks, in the animals that showed marked loss of intestinal function, acinar tissue that stained normally was seldom found except as an isolated island in one of many sections.

This phenomenon of gradual failure of food absorption after evulsion of the pancreatic ducts can perhaps then be explained as Abelman did it. He suggested that, *first* there is absorption of the obstructed enzymes of the pancreas into the blood stream from whence they act on the intestine and *second* there is a gradual disappearance of the enzymes as the pancreas atrophies. It would seem that if an additional hormone is present in the internal secretion of the pancreas it should not be lost with the pancreatic juice of animals with complete pancreatic fistulas.

In all of the animals that showed a marked loss of fat in the feces much of the fat was present as fatty acids which shows that there was some splitting of fat. Neutral fat predominated only when the fat diet was fed, but in such experiments the total amount of free fatty acid excreted was more than that found in normal dogs, and was equal in amount to that found when diets less rich in fat were used. This suggests that the nature of the fat excreted when the fat rich diet was given was of interest. One would expect that the fats of low melting point would be absorbed in greater amounts than those of the higher melting points, and that then the fecal fat would have a higher melting point than that of the combination of fats fed. Contrary to this expectation the fat excreted was liquid at room temperatures. The finding of low quantities of fat in the blood and the absence of a marked postprandial rise of fat in the blood may also

be considered as indicating diminution of fat absorption from the intestine.

The nitrogen excretion in the feces was increased in experimental pancreatic deficiency states. It was found to vary with the bulk of the feces and it bore no relation to the protein content of the diet. In actual fact it appeared to be less when the diet was rich in protein, the bulk of the stool being least when this diet was employed. Our figures do not indicate any failure of protein digestion or absorption, but they do emphasize the fact that considerable nitrogen may be excreted in the stool when the bulk of the feces is large.

## DISCUSSION

It seems obvious from this work that when the pancreas is entirely destroyed or cut off from the bowel there is a marked disturbance in digestion. When the pancreatic juice is being diverted to the outside of the body through a fistula again there is a marked defect in digestion. Apparently under these conditions there is no tendency of the pancreatic secretion to force its way into the bowel through small extra ducts. In cases in which the main duct is tied or evulsed it seems probable that small amounts of secretion still manage to get into the bowel from small areas of remaining pancreatic tissue. In such cases at necropsy one can often find small nubbins of pancreas connected to the bowel with strands of tissue which apparently are ducts. If this reasoning is correct we have an explanation for most of the conflicting results which are found reported in the literature.

Incidentally, these experiments make it seem rather probable that rarely is there any disturbance in digestion due to disease of the pancreas. The factor of safety is so enormous that a demonstrable disturbance in digestion comes only after the pancreas is practically entirely destroyed.

## SUMMARY

The influence of experimental pancreatic deficiency on the utilization of food by dogs was determined. Following either complete pancreatectomy, the production of a complete pancreatic fistula or evulsion of the pancreatic ducts, there was a marked loss of fat and carbohydrate in the feces. An increased excretion of fecal nitrogen was related to the increased bulk of

TABLE V  
*Neutral fat of plasma (in milligrams per 100 cc.) of dogs with fat diet*

24*	Hours Post Cibus					Fecal Fat, Per Cent of Diet Fat	Remarks
	3	6	12	15	24		
136	206	211	195	201	206	4.5	Normal on fat diet 2 weeks.
150	195	193	116	195	113	4.6	Normal on fat diet 2 weeks.
376	226	177	180	296	210	4.3	Normal on fat diet 6 weeks.
366	324	270	216	286	271	3.9	Normal on fat diet 6 weeks.
45	24	44	54	32	40	30.0	Evulsion of pancreatic ducts.
32	40	31	28	41	25	38.0	Evulsion of pancreatic ducts.
36	25	26	24	119	140	72.7	Ducts evulsed; raw pancreas in diet.
25	32	49	36	16	19	77.8	Ducts evulsed; pancreatic juice in diet.
38	68	122	56	122	112	42.0	Complete pancreatic fistula.

\*Anterior.

the feces which was less when diets rich in protein were employed.

The loss of utilization of fat and carbohydrate appeared immediately following removal of the pancreas or the production of a complete pancreatic fistula. Such loss was not seen in dogs following evulsion of the pancreatic ducts; in them it came only after several weeks had elapsed. The gradual failure of food utilization in these animals appeared to parallel the degenerative changes which occurred in the acinar tissue

of the pancreas. It would appear that enzymes sufficient for the normal utilization of foodstuffs may be absorbed from the obstructed pancreatic ducts. Incomplete pancreatic fistulas or incomplete evulsion of the pancreatic ducts produced no detectable alteration in the utilization of food. Gross alterations of the digestive functions appear only in the complete absence of the external pancreatic secretion, and small amounts of pancreas are adequate to maintain complete digestion.

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## IV. Substitution Therapy in Experimental Pancreatic Deficiency\*

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SOME of the earlier investigators of the role of the pancreas in the utilization of food attempted to correct experimentally produced steatorrhea and creatorrhea by the administration of raw pancreas, pancreatic extracts and pancreatic juice. As early as 1890, Abelman demonstrated that the feeding of raw pancreas to depancreatized dogs resulted in improved utilization of these foodstuffs. Sandmeyer, using

larger quantities of raw pancreas, was able to correct the fecal loss of fat and nitrogen completely in partially depancreatized animals. Lombroso (10, 11) attempted to replace both qualitatively and quantitatively the pancreatic juice in the intestinal canal of dogs with pancreatic fistula and with occluded pancreatic ducts. He observed a slight improvement in protein utilization, less in carbohydrate, and no increase in the use of fat. Commercial pancreatic extracts were investigated by Pratt, Lamson and Marks, who employed dogs in which the pancreas had been completely separated from the duodenum. The ad-

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‡Division of Experimental Medicine, The Mayo Foundation. Submitted December 10, 1939.

ministration of "pankreon" to one of these animals reduced the fecal loss of fat from 88.4 per cent to 51.5 per cent, while the loss of nitrogen in the feces fell from 78.0 per cent to 38.0 per cent. "Holadin," another commercial preparation, was said to be effective. Cruickshank fed raw beef pancreas to totally and partially depancreatized dogs, and he observed marked improvement in food utilization in all the animals. Furthermore, this investigator noted an increase in the amount of fatty acids in the feces as the result of administration of raw pancreas.

More recently, the therapeutic value of various pancreatic enzymes and extracts has received further experimental investigation. Selle and Moody in 1937 studied the influence of "pancreatin," an extract of whole pancreas, on the fecal excretion of depancreatized dogs. They reported a 25 per cent to 60 per cent reduction in the bulk of the feces and a marked increase in the elimination time of food when pancreatin was added to the diet. In addition, a definite increase in the utilization of protein resulted. Fat utilization, on the contrary, was actually decreased as the result of pancreatin therapy, according to these workers. Beazell, Schmidt and Ivy, employing dogs with divided pancreatic ducts, found that with a high carbohydrate diet the dried feces consisted of 24.2 per cent carbohydrate. Taka diastase, in daily amounts of 25 gm., caused a 50 per cent reduction in fecal carbohydrate, malt extract in equivalent amounts resulted in a 45 per cent reduction, while "pancreatin," in an enteric coated form, was as effective as the taka diastase. Carbohydrate balance studies were not carried out.

Clinical application of enzyme therapy and organo-therapy has yielded, in most cases, encouraging results. Hirschfeld, Solomon and von Ehrmann have reported a beneficial effect of pancreatic extract therapy in cases of pancreatic steatorrhea. Mosenthal and Gross fed raw beef pancreas to patients with pancreatic insufficiency, and observed a diminution in the fecal loss of fat and nitrogen. Both failed to secure this response with "pankreon." Bargen, Bollman and Kepler have recently reported the beneficial effect of an extract of canine pancreatic juice in certain cases of pancreatic diarrhea.

According to Long and Muhleman, the enzymic activity of most commercial pancreatic preparations is too slight for them to be of practical value. As Fenger and Hull demonstrated, the lipolytic and amylolytic potency becomes materially diminished in six to twelve months, although tryptic potency is retained. Silverman, Denis and Leche determined the effect of various commercial extracts on the enzymic activity of the duodenal contents. They found only a slight increase in the lipolytic and amylolytic activity, but a substantial increase in tryptic activity.

#### METHODS OF INVESTIGATION

The technic of conducting five-day metabolic experiments has been previously described (4), and the same high fat, high carbohydrate, high protein and standard diets were employed. Likewise, the same analytic technic for fecal fat, carbohydrate and protein determinations was utilized.

#### RESULTS

Pancreatic juice was secured from dogs with pancreatic fistulas. The juice from different animals was

pooled, and it was used within thirty-six to forty-eight hours. It was administered by means of a stomach tube immediately before and one hour after the daily meal. Activation of the pancreatic juice by the addition of fresh duodenal scrapings was carried out in some experiments. High jejunal fistulas, of the Mann-Bollman type, were established in several dogs, and the juice was given by this route. Fresh pancreatic juice in daily amounts of 20 cc. to 300 cc. was administered as a single dose and in divided doses throughout the day to dogs with evulsed pancreatic ducts in sixteen experiments.

The sixteen experiments were conducted using the following diets: Fat, seven; standard diet, four; carbohydrate, three; protein, two. In no instance did the addition of pancreatic juice reduce the fecal loss of fat from the fat diet. A small decrease of fat excretion was found in one animal receiving pancreatic juice while on the standard diet and in one on the protein diet. A definite reduction from 95 per cent of the ingested fat in the feces of the untreated animal to 55 or 50 per cent occurred when pancreatic juice was given to animals receiving the carbohydrate diet. Within the limits studied, the volume or activation of the pancreatic juice given did not influence the results.

In each of these experiments there was a conspicuous decrease in the amount of carbohydrate lost in the feces. The reduction in the loss of carbohydrate was about 25 per cent for each 50 cc. of fresh pancreatic juice used when the diet contained large amounts of carbohydrate; so that values approximately normal were obtained where more than 200 cc. of pancreatic juice were given. The fat and protein diets contained small amounts of carbohydrate and no definite reduction of the loss of this carbohydrate was obtained except when 300 cc. was given daily.

Reduction in the amount of nitrogen lost in the feces when pancreatic juice was given occurred only in those experiments where there was a large reduction in the loss of carbohydrate. The loss of nitrogen corresponded to the volume of the stool which was smaller when the carbohydrate utilization was improved.

*Influence of precipitated pancreatic juice.* Fresh canine pancreatic juice was precipitated as described by Bargen, Bollman and Kepler. The powdered precipitate was placed in capsules each of which contained the amount derived from 20 cc. of pancreatic juice. The capsules were administered orally, half the daily dose immediately before feeding and the remainder one hour later. Eight experiments using the equivalent of 100 to 200 cc. of pancreatic juice added to the diets of dogs with complete evulsion of the pancreatic ducts were studied. Only in one experiment was there any reduction of the amount of fat, carbohydrate or nitrogen loss in the feces. The reduction in this experiment was not great enough to be of significance.

*Influence of lipocaine, pancreatin, trypsin, taka diastase and bile salts.* Lipocaine prepared according to the method of Dragstedt, van Propaska and Harms was administered orally in amounts equivalent to 300 gm. of pancreas each day to dogs with evulsed pancreatic ducts. No significant alterations in the fecal loss of foodstuffs were observed.

Two grams of commercial pancreatin were given daily by mouth to two completely pancreatectomized

dogs and to one dog after complete evulsion of the pancreatic ducts. In each experiment the fecal loss of fat and nitrogen was unaffected while a reduction of approximately half of the carbohydrate loss occurred in each animal.

Trypsin, 400 mg. daily, taka diastase, 400 mg. daily, and bile salts, 2 gm. daily, were given to animals with evulsed pancreatic ducts. In no experiment was there a significant reduction in the loss of any of the foodstuffs.

Daily cross transfusion of 350 cc. of blood from a normal dog to a dog with evulsed pancreatic ducts had no effect on the fecal loss of foodstuffs.

*Influence of pancreas in the diet.* The influence of raw pancreas on the utilization of food was investigated in eleven experiments on dogs with evulsed pancreatic ducts and in five studies on depancreatized animals. Fresh beef pancreas was obtained in the frozen state. The excess fat was removed and the pancreas cut into small pieces. These, in amounts of 25, 100, 200 or 250 gm. daily, were mixed with the diets used.

When the larger amounts of pancreas were used there was only a slight decrease in the fecal loss of fat from the fat diet. With the other diets which contained less fat the reduction of the loss of fecal fat was definite but in all cases several times the normal loss occurred.

The carbohydrate loss in the feces was greatly reduced when pancreas was added to the diet in all experiments. When more than 100 gm. of pancreas was given daily the carbohydrate loss was reduced from 25 to 35 per cent without treatment to 1.6 to 3.1 per cent except when the carbohydrate diet was used. In this case the carbohydrate loss was greatly reduced but did not reach normal values.

The fecal loss of nitrogen was much reduced in all

cases when pancreas was added to the diet and there was a corresponding reduction in the bulk of the stool.

## COMMENT

Replacement therapy definitely reduced the loss of carbohydrate in the feces of animals after complete pancreatectomy or evulsion of the pancreatic ducts when large amounts of carbohydrate (cracker meal) were included in the diet. Pancreatic juice, raw pancreas or pancreatin preparations appeared to be effective, but normal values of carbohydrate were obtained only when large amounts were given. Concomitant with the improvement of carbohydrate utilization the bulk of the feces was decreased and the amount of nitrogen lost was reduced. There seemed to be no direct effect of the replacement therapy on the amount of nitrogen that appeared in the feces. In some experiments it also appeared that the fat utilization was improved slightly when the carbohydrate utilization was nearly at normal levels.

The utilization of fat which had been markedly decreased after pancreatectomy or evulsion of the pancreatic ducts was not materially influenced by any one of the treatments we tried. Several attempts were made to prevent possible destruction of activity of the pancreatic juice, but even the continuous instillation of pancreatic juice into the upper jejunum by way of a jejunal fistula gave no better results than the single administration of the daily dose by stomach tube. The failure of replacement therapy was in marked contrast to the normal utilization of foodstuffs when but small amounts of pancreatic juice drain into the intestine as in animals with incomplete pancreatic fistulas or incomplete evulsion of the pancreatic duct. It is obvious that we failed in all of our attempts to supply even a small amount of the pancreatic secretion needed to maintain normal secretion.

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## Role of Food Intake in the Restoration of the Liver Following Partial Hepatectomy in Albino Rats

By

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THE purpose of this paper is to present data relative to the amount of food ingested by partially hepatectomized rats throughout their postoperative course, in order to report a correlation which was found between the extent of restoration of the liver and the amount of food ingested. Two series of partially hepatectomized animals were used; one group was permitted to eat ad libitum and the other was given a constant amount of food daily by means of a stomach tube.

The ability of the hepatic remnant to regenerate following partial hepatectomy is well known. Numerous attempts have been made to determine the factors which control the restoration, and a fine review of the literature is available in the article by Brues, Drury and Brues. The role of the portal blood supply has been investigated and its importance established. Franseen, Brues and Richards studied the reaction of restoration of the liver in hypophysectomized animals, as did Higgins and Ingle. Both groups of investigators obtained essentially similar results in that the hepatic restoration occurred to a less extent in the hypophysectomized animals. Higgins and Ingle experienced difficulties in controlling the dietary intake of their animals as the hypophysectomized, partially hepatectomized animal eats less than the normal animal does. They found that the regeneration of the liver seemed to depend on the amount of food consumed.

A very important contribution to the knowledge of the role of diet in hepatic restoration was made by Brues, Drury and Brues. These workers found a difference between the restoration of the hepatic mass and the increase in the actual number of hepatic cells during the restoration. They learned that lesser amounts of hepatic tissue were restored when the animal was fed a high carbohydrate or a high protein diet than when it was fed a standard diet. The largest hepatic fragments which were observed by them occurred in the group of animals fed a high fat diet. The smallest fragments were obtained in a group of animals which had been fasted. The increase in the number of hepatic cells was about the same on either the high protein, the high carbohydrate or the standard diet; it was least on the high fat diet, even less than in the fasted animals. McLennan and Jackson showed that the weight of the liver of the rat during inanition decreases at a rate greater than that of the loss in total body weight.

We have thought it desirable to study the role of the amount of food ingested, in hepatic restoration

following partial hepatectomy, in order to furnish control data to refer to when one is dealing with experimental conditions which in themselves affect the appetite.

### METHOD

The animals used in these experiments were inbred male albino rats of the Wistar strain. The average weight of the thirty-six animals immediately prior to partial hepatectomy was  $209 \pm 35$  gm.

Two series of animals were used and each series was maintained on a different dietary regimen. The first group ate a powdered commercial diet ad libitum. The amount eaten during each twenty-four hour period was calculated. The animals were housed in cages in groups of threes. The constituents of this diet were as follows: protein 20 per cent, fat 4 per cent, carbohydrate 46 per cent (1 gm. = 0.77 cal.). The second dietary regimen consisted of administering three times daily a constant amount (6 cc.) of specially prepared diet by means of stomach tube. This diet was composed of protein 16.7 per cent, fat 21.1 per cent and carbohydrate 46.7 per cent (1 cc. = 3.29 cal.).\* The rats were fed this diet for one week prior to operation and for the entire postoperative period of twenty-one days during which observations were made; no other food was allowed this group. Both diets were adequate as to the essential vitamins. The animals in both groups had access to water at all times and the daily intake was followed. The animals were fasted for eighteen hours prior to operation. The commercial diet was made available to the group on this diet immediately after operation, and tubing was resumed within six hours after operation in the group artificially fed.

**Operation.** Partial hepatectomy was performed under light ether anesthesia according to the technic of Higgins and Anderson whereby the bifurcate median and left lateral lobes were removed, and the right lateral and caudate lobes were left in place.

**Estimation of liver size.** It is impossible to determine the exact weight of the remnant of the liver following partial hepatectomy; however, it is possible to guess at it, since the weight of the remnant bears a rather close relationship to the total weight of the liver. An approximation of this weight was made by weighing the portion ordinarily removed during partial hepatectomy, and that component left at operation, in a group of ten animals of a range of body weight similar to that of the experimental group. By this method we learned that about 32 per cent of the total weight of the liver was left behind at operation,

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\*The authors are indebted to Dr. L. F. Samuels of the University of Minnesota for the formula for this diet.

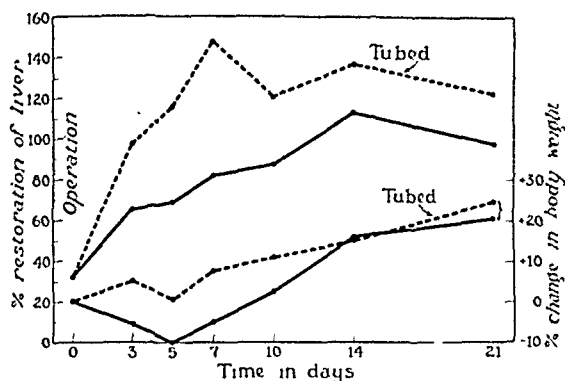


Fig. 1. Comparison of the relative degree of restoration of the liver and the percentage change in body weight following partial hepatectomy in animals on two separate dietary regimens. The degree of restoration is expressed in terms of the calculated original weight of the liver. The percentage change in body weight was calculated from the body weight prior to partial hepatectomy and the body weight at necropsy.

so that this figure was used in estimating the amount of hepatic tissue restored in terms of the original weight of the liver during the various intervals following operation. The animals were killed by exsanguination following light ether anesthesia on the third, fifth, seventh, tenth, fourteenth and twenty-first days after operation. The hepatic remnant at these intervals was removed, freed of blood by blotting, and weighed, and the specimens were fixed in 10 per cent solution of formaldehyde. Microscopic sections were examined after being stained with hematoxylin and eosin and scarlet red.

### RESULTS

**Commercial diet.** The curve of restoration of the liver of rats on the commercial diet which was obtained following partial hepatectomy in these experiments was similar to those previously reported (5). The hepatic remnant increased in size progressively until the tenth to twelfth day at which time a mass amounting to about 100 per cent of the original weight of the liver was attained. A slight increase in liver mass occurred on the fourteenth day but it decreased to 100 per cent by the twenty-first day (Fig. 1). Examination of the data obtained with reference to the daily food intake throughout the postoperative period of twenty-one days discloses that the intake decreased during the first few days of the postoperative period and the preoperative level was not reached until the eleventh day. At this time the hepatic remnant had become restored to approximately 100 per cent of its original size. The daily water intake, which was slightly decreased during the early postoperative period, likewise returned to its preoperative level at the tenth or eleventh day. The loss in body weight which had occurred after operation was regained at the tenth day (Fig. 2). Thus it can be seen that the curve of restoration of the hepatic remnant follows rather closely the curve of daily food and water intake as well as the trends in the body weight.

**Artificial feeding.** On examining the curve of restoration of the liver in the group of animals which was fed a constant amount of food by tube daily throughout the entire postoperative period, marked differences were found in the rate and degree of restoration as

compared with that observed in animals fed the commercial diet. In the tubed group, the results of the early postoperative decrease in appetite were avoided by forced feeding. In this group of animals the original weight of the liver was restored by the third postoperative day, a week earlier than in the animals that ate what they pleased. In the tubed group the peak of restoration (148 per cent) was reached by the seventh day after which the level decreased to 120 per cent; it tended to remain at this figure throughout the remainder of the twenty-one day period. The post-operative loss in body weight which occurred in the commercial diet group was avoided in the tubed group (Fig. 1).

### COMMENT

The data presented indicate some correlation between the amount of food ingested and the degree of restoration of the hepatic remnant following partial hepatectomy. In the animals that ate what they pleased, the loss in body weight following operation occurred simultaneously with a decreased appetite 100 per cent of the original weight of the liver having been restored by the time appetite and body weight had returned to normal. Forced feeding of a group of partially hepatectomized animals prevented the loss of weight which occurred in the early postoperative period in the animals that ate what they pleased, and the forced feeding regimen resulted in an earlier restoration of the hepatic remnant as well as a greater degree of restoration than in the group fed on the commercial diet.

However, examination of the microscopic sections stained with scarlet red disclosed that the hepatic remnants of the animals which were tubed contained considerable amounts of stainable fat throughout the entire twenty-one day period. The fat was scattered diffusely throughout the entire lobule, but occurred in greatest density about the central vein. No stainable fat was detectable in the microscopic sections prepared from the livers on the commercial diet. This indicates, at least, that the increase in restoration of hepatic mass in animals on the tubing regimen was not a purely cellular one but was due in part to an accumulation of fat in the hepatic cells. This is in accordance

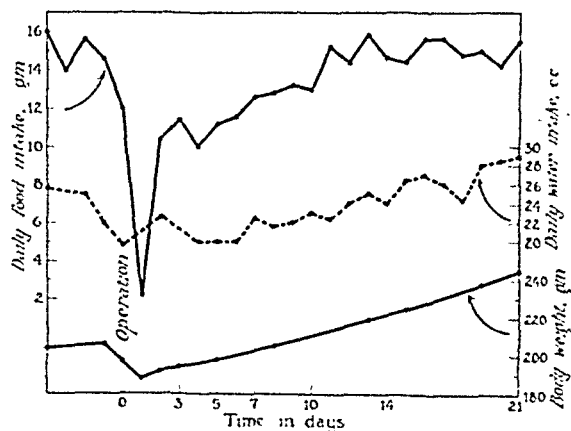


Fig. 2. The average daily food and water intakes of a group of eight rats on the commercial diet before and for twenty-one days after partial hepatectomy bear a close relationship to the trends in the average body weight.

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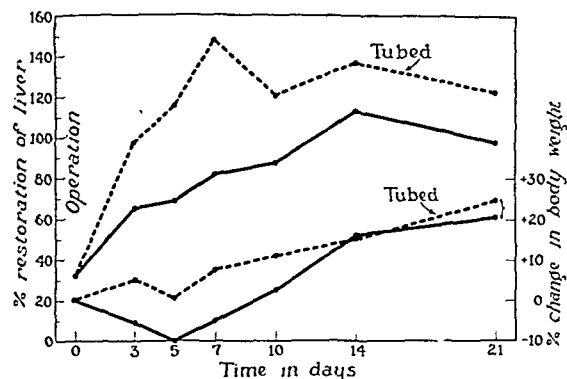


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compared with that observed in animals fed the commercial diet. In the tubed group, the results of the early postoperative decrease in appetite were avoided by forced feeding. In this group of animals the original weight of the liver was restored by the third postoperative day, a week earlier than in the animals that ate what they pleased. In the tubed group the peak of restoration (148 per cent) was reached by the seventh day after which the level decreased to 120 per cent; it tended to remain at this figure throughout the remainder of the twenty-one day period. The postoperative loss in body weight which occurred in the commercial diet group was avoided in the tubed group (Fig. 1).

## COMMENT

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However, examination of the microscopic sections stained with scarlet red disclosed that the hepatic remnants of the animals which were tubed contained considerable amounts of stainable fat throughout the entire twenty-one day period. The fat was scattered diffusely throughout the entire lobule, but occurred in greatest density about the central vein. No stainable fat was detectable in the microscopic sections prepared from the livers on the commercial diet. This indicates, at least, that the increase in restoration of hepatic mass in animals on the tubing regimen was not a purely cellular one but was due in part to an accumulation of fat in the hepatic cells. This is in accordance

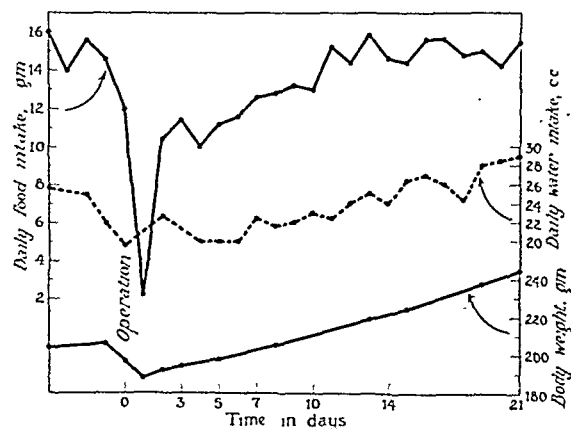


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with the work of Brues, Drury and Brues who found that on various types of diets in which the percentages of predominating constituents were varied, there was no correlation between the degree of restoration in mass of hepatic tissue and the cellular restoration.

### CONCLUSIONS

1. There appears to be a correlation between the amount of food ingested and the degree of restoration of hepatic mass following partial hepatectomy.

2. The loss in body weight of animals that eat what they please can be prevented by forced feeding, which procedure effects a more rapid and greater degree of hepatic restoration.

3. The apparently greater degree of hepatic restoration on a forced feeding regimen, to a certain extent at least, is due to an accumulation of fat in the hepatic cells.

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## The Treatment of Amebiasis by a Combined Method—Statistical End Results\* (Oral Administration of Carbarsone and Retention Enemata of Chiniofon)

By

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### INTRODUCTION

THE most effective amebicidal drug now known fails in 10% of the cases to produce a permanent cure, when used alone as single drug therapy, and in a single course of treatment. Furthermore, any plan of drug therapy which may require repeated courses is not ideal, first, because, in the case of some of the most effective amebicidal drugs, the administration of repeated courses increases the risk of toxic drug reactions, and, secondly, because it is not possible to maintain with all patients the continued contact necessary for repeated drug treatment. Therefore, a simple method of combined drug therapy which has reduced the therapeutic failures from 10% to 3%, with a single course of treatment, and without risk to the patient if properly employed, seems worth reporting.

Before describing this combined method of treatment, and the results obtained from its use, it seems advisable to review briefly the therapeutic effectiveness and toxicity of each of the four outstanding amebicidal drugs. This discussion concerns the use of each drug when used alone in single drug therapy.

### THERAPEUTIC EFFECTIVENESS AND TOXICITY OF THE FOUR OUTSTANDING AMEBICIDAL DRUGS

#### I. EMETINE

Craig, in his classical monograph (1) upon amebiasis, has noted that emetine hydrochloride, when used alone, produces not more than 15% of permanent cures. This figure represents the consensus of opinion of experienced workers in this field. It is recognized that emetine is moderately effective in destroying the vegetative amebae within the tissues, but not in eradicating the cysts. It is especially effective in relieving

promptly the diarrhea and tenesmus in severe cases of acute amebic dysentery. Furthermore, the value of emetine in cases of amebic hepatitis and abscess is generally appreciated.

Craig (1) and Reed (2), on the other hand, have stressed the evidence accumulated by various workers that emetine not infrequently produces an acute or chronic toxic degenerative effect upon the myocardium. This is especially true if given in too large doses, or in repeated courses. In this clinic six years ago a case of marked tachycardia, with cardiac embarrassment lasting six weeks, was noted in a previously healthy young woman who had received one grain of emetine hydrochloride subcutaneously each day for only six days before the cardiac symptoms developed. This patient had presented no evidence of previous cardiac damage. (The course of emetine given was less than two-thirds as long as the 10 to 12 day course usually given, and often referred to in the literature as the proper course to administer).

#### II. CARBARSONE (Carbaminophenyl arsonic acid)

Carbarsone is regarded generally as the most effective and least toxic of the various arsenical amebicidal drugs.

In 1934 Anderson and Reed reported having treated 330 cases of amebiasis with carbarsone alone. They were successful in eliminating the infection in 90% of their cases (3, 4 and 1). Furthermore, these authors (3) reported that only one of the 330 patients failed to tolerate the drug. This patient, who had an enlarged liver before treatment, was given a single course of 5.0 grams of carbarsone, and developed a transient catarrhal jaundice. Excluding cases with liver damage, these authors feel that carbarsone is a drug with a good margin of safety. Due to the slow excretion of the drug, they advised the precaution of a ten day period of rest before a second course is given. However, only a small percentage of their cases

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received a second course. These authors also reported a desirable tonic effect from carbarsone. In this clinic in 1934 a group of amebiasis cases was treated with carbarsone alone. The percentage of cures was 89%, or almost identical with that reported by Anderson and Reed.

In the 104 cases reported in this communication in which the patient received a single standard course of carbarsone by mouth and chiniofon enemata simultaneously, there was no instance of any toxic arsenical reaction. In two of the earlier cases, treated by carbarsone alone, who received twice the usual total dose of the drug, there was an arsenical reaction. One of these patients, with very acute symptoms of amebic dysentery in 1934, received  $\frac{1}{4}$  gram of carbarsone twice a day for ten days; and after a rest interval of only two days he received a second similar ten day course of carbarsone treatment. This patient developed a mild catarrhal jaundice, from which he completely recovered in a short time. The second patient received 0.50 gram of carbarsone, instead of the usual dose of 0.25 gram, twice a day for ten days. This patient developed a transient mild peripheral neuritis, from which recovery was prompt and complete.

Since 1934 it has been the policy of this clinic, therefore, to avoid giving more than the single standard course of carbarsone, viz.,  $\frac{1}{4}$  gram before breakfast and supper each day for ten days. The experience of this clinic coincides with the experience of others that carbarsone is a safe drug if circumspectly administered in the above manner.

### III. CHINIOFON ("Anayodin" or "Yatren") (sodium iodohydroxyquinoline-sulphonate)

Craig (1), Mackie (5) and others who have used chiniofon extensively, have reported that it is a non-toxic drug, even when used in repeated courses, if administered properly in therapeutic dose of from two to four 0.25 gm. tablets three times a day for eight to ten days.

Craig (1) also reported that the majority of cases of amebiasis obtained permanent cure following a single course of chiniofon. He stated, however, that in some cases repeated courses of treatment with chiniofon were necessary; and a few cases required subsequent treatment with carbarsone. Because of its safety and efficiency Craig (1) has used chiniofon rather routinely in his treatment of amebiasis. In the acute cases with marked dysentery, he also used emetine at the onset of the treatment to obtain prompt symptomatic relief.

When administering chiniofon orally it is important to give it in some such form as "Anayodin." In this preparation the chiniofon tablet is covered with an enteric coating, which carries it through the stomach without change, but allows it to break down readily in the intestine. When chiniofon is given by retention enema the powdered form should be used in preparing the 2½ per cent solution.

### IV. VIOFORM (iodochlorhydroxyquinoline)

This drug is similar chemically to chiniofon, but contains more iodine than chiniofon, and also includes a chlorine atom. In experimental work with monkeys Anderson and Koch (6) found vioform more effective than chiniofon in promptly and completely eradicating *E. histolytica*. In 1933, David, Johnstone, Reed and Leake (7) first reported the treatment of human amebiasis with vioform; and they also found it some-

what superior to chiniofon. These authors advised giving  $\frac{1}{4}$  gram t.i.d. for ten days, and then, after a rest period of seven days, gave a second similar course. They obtained 74.5% of cures in 47 cases treated with vioform. These authors felt that the percentage of cures would have been higher if there had not been some probable cases of reinfection in the group, resulting from poor hygienic environment.

Reed (2) reported that vioform is somewhat less effective than carbarsone. He states, however, that it is an excellent drug to use in alternation after the arsenical drug, carbarsone, in those cases needing follow-up treatment because of a recurrence.

Unlike chiniofon, vioform cannot be used for retention enemata, since it is more irritating to mucous membrane surfaces than chiniofon. When given orally vioform should be given at meal time. If given between meals, occasionally it may cause rather marked irritation of the gastric mucosa.

The toxicity of vioform, Anderson and Reed (3) reported, is slight or absent, unless one exceeds the usual therapeutic dose of 0.25 gram three times a day for ten days, with repetition of the same course after a week's rest. Furthermore, in certain severe and old relapsing cases Reed and his associates (3 and 7) gave more than two such courses. According to their experience this can be done with safety.

The experience of this clinic with vioform has coincided with that of Reed and his associates, in indicating the high degree of amebicidal effectiveness and the non-toxicity of this drug in therapeutic doses. No case of systemic reaction to vioform has been observed. This drug is most valuable in the follow-up treatment of the occasional case presenting a recurrence of the infection after carbarsone administration.

## COMBINED DRUG THERAPY

There are several reports of combined drug therapy in the literature, which are of special interest. In 1935 P. W. Brown (8) reported the results obtained over a fifteen year period in treating 834 cases of amebiasis. He preferred a combination of emetin and the arsenical drug, treparsol, to other methods of drug therapy. Brown reported 91.1% of favorable results.

Mackie (5), in an admirable article dealing with the pathology and treatment of amebiasis, reported "excellent results" from intensive combined therapy in those cases failing to respond to ambulatory, single drug, chiniofon therapy. This combined treatment consisted of the simultaneous administration of emetine given hypodermically and chiniofon administered both orally and by retention enemata.

## METHOD OF COMBINED DRUG TREATMENT EMPLOYED

The 104 cases of amebiasis included in the following study received a uniform single course of combined drug treatment. This included the oral administration of a standard course of 0.25 gram of carbarsone before breakfast and supper daily for ten days. Simultaneously a small chiniofon retention enema was given by a special technique (described below) every other morning during this ten day period for a total of five such treatments. A cleansing saline enema of about 750 cc. preceded each chiniofon retention enema. (Care was taken not to overdistend the colon). On the mornings of the enemata, the morning dose of car-

barsone was given after the cleansing saline enema, for the reason stated below.

There is a sound and highly desirable rationale for the simultaneous administration of these two particular amebicidal drugs. The fact that these very effective agents are so different chemically, and at the same time are practically free from any unfavorable reaction, if properly employed, has made it possible to administer them simultaneously in full therapeutic doses, and thus obtain the full combined effect. Furthermore, the fact that chiniofon can be administered safely and advantageously as retention enemata, and is known to be effective in killing both the encysted and vegetative forms of amebae, renders it an ideal drug for combination with the oral administration of carbarsone.

As noted previously, carbarsone, apparently the most effective of the present known amebicidal drugs, very rarely produces any toxic reaction when given properly in a single standard course. However, it may incite occasionally a transient hepatitis, if given in repeated courses. This fact renders it desirable to combine with carbarsone another effective drug, which is entirely non-toxic, such as chiniofon. The combined, simultaneous action of these two drugs is so effective that a second course of carbarsone is unnecessary.

As a conservative precaution, all patients receiving the single standard course of carbarsone have been instructed to report promptly any new symptom developing during carbarsone therapy. This seems important, even though none of the 104 cases reported in this study exhibited any unfavorable arsenical reaction. In case any patient should develop a suspected arsenical reaction, the carbarsone should be stopped, and intravenous glucose with increased fluid intake should be started promptly to provide a margin of safety.

The use of antiseptic retention enemata in the treatment of chronic ulcerative colitis was discarded in this clinic a number of years ago, as it was in most other gastro-intestinal clinics. However, the use of retention enemata in amebiasis has been instituted as an advance. The rationale is as follows. In amebiasis there are many vegetative and encysted forms of amebae in the lumen of the intestine, in the fecal contents, and on the surface of superficial ulcers. These organisms, as well as those in the deeper layers of the intestinal wall, must be killed if reinfection by direct contact is to be avoided. The elimination from the colon of the liquid and solid fecal contents every other day, by the use of a cleansing saline enema, followed by the introduction of a concentrated, amebicidal retention enema should supplement the oral administration of any amebicidal drug. If the enemata are given in the morning, time will have been afforded for the full effect of the oral drug given the previous day. To avoid any premature elimination, by the cleansing enema, of the oral drug given the same morning, the carbarsone should be given after the enema.

A special technique has been utilized for the administration of the chiniofon enemata. It is designed to carry the chiniofon solution around to the ascending colon and caecum, the generally recognized major site of amebic lesions and infection. On the morning of each chiniofon retention enema treatment, breakfast is omitted. At 8:00 a.m. a cleansing saline enema of about 750 cc. is administered, with a technique to in-

sure a thorough cleansing of the entire colon and an elimination of the saline solution. This procedure is intended to facilitate direct contact of the subsequent concentrated chiniofon enema with amebic ulcers in the caecum and other portions of the colon and rectum. At 9:00 a.m. 250 cc. of a 2.5% aqueous solution of chiniofon is given to the patient in the knee-chest position. This position is maintained for five minutes, in order to facilitate the prompt passage of at least part of the small chiniofon enema beyond the opened splenic and hepatic flexures into the ascending colon. After remaining in this position for 5 minutes, the patient drops immediately onto the right side where he or she remains for half an hour. The purpose of this shift in position is to aid in the temporary retention of chiniofon in the caecum and ascending colon. Instructions are given then to turn onto the back for half an hour, subsequently onto the left side for half an hour, and finally onto the back again, where the patient remains until 1:00 p.m. or longer. This total four hour period permits the absorption of the chiniofon enema. (Most patients are able to retain and absorb this enema). These chiniofon treatments are given under the supervision of a specially instructed nurse, either in the out-patient or in-patient department of the hospital. At the onset of treatment of the acute cases, the diarrhea has been controlled sufficiently well for retention of the small chiniofon enema, by frequent doses of camphorated tincture of opium.

A barium enema of 250 cc. only was given to a small group of patients, using the above special technique for administering chiniofon retention enemata. Fluoroscopic and film observations indicated that part of the barium promptly and consistently reached the ascending colon and caecum in this group of patients within the initial five minute period; and this portion of the barium tended to remain in the ascending colon as long as the patient remained on the right side. The validity of the chiniofon enema technique is based finally, therefore, upon these barium observations and on the therapeutic results obtained, and not simply upon the a priori reasoning referred to above.

It has not become necessary to give emetine to any of this group of 104 uncomplicated cases, which included the various clinical types of amebiasis. In some of the acute cases several extra days were required before complete symptomatic relief of the tenesmus and diarrhea was obtained, as compared with the very prompt symptomatic relief obtained from emetine. However, on account of its toxicity and relative ineffectiveness in producing permanent cures, emetine no longer is used in this clinic, except in the occasional cases complicated by amebic hepatitis or abscess. Although the occasional use of emetine for prompt symptomatic relief can be justified in the very severe cases of acute amebic dysentery, its routine use in treating amebiasis no longer seems justified, for the two reasons referred to above.

In the rare cases exhibiting a recurrence of amebiasis after the above type of combined therapy, vioform has been administered orally according to the method advised by Reed and his associates (7) and outlined above.

General supportive measures, such as bed rest, high protein and high vitamin diet, and other adjuvants

needed in addition to drug therapy, in the cases of active amebiasis, should not be omitted.

### CLINICAL MATERIAL UTILIZED

The clinical material for this study consisted of an unselected group of 104 uncomplicated cases of amebiasis. These 104 cases may be divided into five clinical subgroups, as noted in Table I.

The first subgroup included 20 cases of acute amebic dysentery, with diarrhea and associated tenesmus in most of these cases. The symptoms in this subgroup were relieved by the amebiasis treatment.

The second clinical subgroup consisted of 19 cases of chronic relapsing amebic dysentery, with a history of previously repeated acute or subacute attacks of dysentery. The symptoms in this subgroup also were relieved by the amebiasis drug treatment. The 39 cases comprising subgroups I and II, (37.5% of the total group of 104 cases), were cases of active amebiasis.

The third subgroup consisted of 25 carrier cases, or more properly designated as latent cases, without any type of colon symptoms. (It is now recognized that the majority of these latent cases have superficial

pin point ulcers (and also colon distress), in 11 months and 12 months respectively after completion of amebiasis treatment, amebae having remained absent from the stools during this entire period. It would seem quite certain, therefore, that *E. histolytica* was not the etiological factor for the "pin point" rectal ulcers in these eight cases.

When one considers that, according to figures commonly cited, at least 5% of the population at large have *E. histolytica* infestation, it is not surprising that a small percentage of patients with chronic irritable colon and chronic ulcerative colitis should harbor amebae. P. W. Brown (8) found the proctoscopic picture of "idiopathic ulcerative colitis" in 8.8% of his 576 patients with amebiasis who received proctoscopic examination. This percentage figure compares closely with the 7.7% in our group. Brown also found that the ulcerative colitis in these cases did not clear up with the therapeutic eradication of the amebae. He arrived at the same conclusion as the authors of this paper, that the amebiasis "played only an incidental role" in this group of cases.

The group of 104 unselected cases utilized in this study apparently represent an average cross section of cases for the temperate zone. Brown (8) reported that 33% of his group "had evidence of active amebiasis." In our group of 104 cases, 37.5%, or the 39 cases in the first two clinical subgroups, represent cases of so-called active amebiasis; and 62.5%, or the 65 cases in the last three sub-groups, were cases of clinically "latent" amebiasis. In this latent group of 65 cases, the 40 cases (38.4%) in the last two clinical subgroups had colonic symptoms not of amebic etiology.

During the evaluation of combined drug therapy, as reported in this communication, the only clinical type of amebiasis not included in the group of 104 cases thus treated was the type complicated by amebic hepatitis or hepatic abscess. As noted above, carbarsone is contra-indicated in the presence of liver damage; and emetine is the drug of choice in treating amebic hepatitis. Intensive chiniofon therapy should be combined with emetin in these cases, to enhance the chance of a permanent cure, in case the patient survives the acute hepatic complication.

During the period of treatment of the 104 uncomplicated cases, two cases of acute hepatitis were seen in this clinic. One of the two cases was treated early and intensively, and recovered completely. The second case was moribund on admission to the hospital, and died almost before treatment had been started. A large hepatic amebic abscess was found at autopsy.

### WARM STOOL FINDINGS

The warm stool specimens were all obtained either by giving a warm, cleansing, normal saline enema, or by administering a saline cathartic orally. In either case the liquid feces from the caecum and ascending colon area were obtained. During the past eight years the warm stool specimens in this clinic have been examined with meticulous care by the same experienced parasitologist. In each one of the 104 cases of amebiasis reported the histolytica strain of ameba was definitely demonstrated. Vegetative amebae were found in a total of 90% of the 104 cases, and the encysted forms in 30%. When either form of *E. histolytica* was demonstrated definitely in the first stool specimen ex-

TABLE I  
*Clinical sub-groups of 104 amebiasis cases\**

	Type of Case (or Sub-Group)	No. of Cases
I	Acute amebic dysentery	20
II	Chronic relapsing amebic dysentery	19
III	Latent amebiasis, without colon symptoms	25
IV	Latent amebiasis, with irritable colon symptoms	32
V	Latent amebiasis, with associated pin-point ulcers of chronic ulcerative colitis	8
	Total cases	104

\*Two cases with amebic hepatitis or hepatic abscess were not included, since they received emetine.

ulcerative lesions in the caecum or ascending colon, even though no symptoms are present).

The fourth clinical subgroup consists of another type of latent amebiasis, occurring in patients with an associated "chronic irritable colon" condition. In this group the characteristic dull, shifting irritable colon distress was not relieved by amebiasis treatment and the disappearance of amebae from the stools. However, it was relieved by subsequent comprehensive irritable colon therapy. This clinical subgroup was discussed in detail by Paulson (9) in his recent communication.

The fifth clinical subgroup (8 cases) consisted of a third type of latent amebiasis, occurring in patients who presented the typical proctoscopic findings of "chronic ulcerative colitis." In these eight cases the rectal ulcers were the numerous, minute or "pin point" lesions characteristic of so-called "idiopathic" chronic ulcerative colitis. These rectal ulcers did not disappear until from three to eight weeks after amebiasis treatment had been concluded, although the amebae had promptly disappeared from the stools in each case. During this interval intensive chronic ulcerative colitis treatment had been instituted when the rectal ulcers failed to disappear within ten days after conclusion of amebiasis treatment. Furthermore, in two of these eight cases there was a return of numerous



amed, as occurred in the majority of cases, no repeat examinations were conducted until after treatment. The stools have been cultured in certain instances, but the main reliance has been placed upon the immediate microscopic diagnosis of the freshly obtained material. The details of the stool findings are summarized in Table II.

PROCTOSCOPIC FINDINGS

In suspected cases of amebiasis it is most important to note in the proctoscopic examination not only

TABLE II

Stool findings in various clinical sub-groups\*

Clinical Sub-Groups	No. of Cases with Cysts and Motile Forms (E.Hist.)	No. of Cases with Motile Forms Alone (E.Hist.)	No. of Cases with Cysts Alone (E.Hist.)
I and II (active)	5	33	1
III, IV, and V (latent)	11	41	13
Total	16	74	14

\*In each one of the 104 cases of amebiasis reported, *E. histolytica* was demonstrated. Motile amebae were found in a total of 90% of cases, and cysts in 30%.

whether ulcers are present, but also whether the ulcers are characteristic of amebic ulceration, or, of chronic ulcerative colitis. In any particular case where ulcers are found, is one dealing with an uncomplicated case of amebiasis, with amebic ulceration in the rectum, or with a case of latent amebiasis associated with a typical chronic ulcerative colitis? In the latter group of cases, with amebicidal treatment and the disappearance of amebae from the stools, one does not expect a prompt healing of the ulcers of chronic ulcerative colitis.

Amebic ulcers are usually quite characteristic. They tend to be discrete. In contrast to the numerous and

TABLE III

Proctoscopic findings in clinical sub-groups of amebiasis

Clinical Sub-Groups of Cases	% of Cases with Amebic Type of Rectal Ulcers	% of Cases with Pin-Point Ulcers of Chronic Ulcerative Colitis	% of Cases with No Rectal Ulcers
I and II	38.5%	0.0%	61.5%
III and IV	3.5%*	0.0%	96.5%
V	0.0%	100.0%	0.0%

\*Majority of clinically latent cases have superficial ulceration of caecum or ascending colon.

characteristic "pin-point" ulcers of chronic ulcerative colitis, often accompanied by marked injection or reddening of the intervening rectal mucosa, amebic ulcers are not as small or numerous, and they are also deeper or "punched out," with an undermined edge. Amebic ulcers usually vary in size from 2 mm. to 7 mm. In the presence of these occasional scattered amebic ulcers, the intervening rectal mucosa usually appears pink and normal, although somewhat glistening, because of the increased production of mucus. The rectal

ulcers of acute bacillary dysentery tend to be pin point in size and to resemble those of chronic ulcerative colitis, except, in the average case, they are less numerous. Usually, therefore, these ulcers also can be differentiated readily from amebic ulcers. (See Table III for proctoscopic findings).

FOLLOW-UP STOOL STUDIES

The routine practice in this clinic has been to examine a warm stool every week for four weeks after completion of combined drug therapy, then every month for five months, and then every six months for a total period of three years, or longer if possible. In this group of 104 cases the period of follow-up stool studies has varied from six months to three and one-half years. The number of cases having various periods of follow-up stool examinations is specified in detail in Table IV. In this prolonged course of follow-up examinations, there was, of course, an occasional omission of a stool examination called for in the schedule. However, in such cases there were subsequent examinations. Furthermore, since the follow-up stool examinations in this clinic have been conducted, as noted above, with meticulous care by the same experienced parasitologist, the negative stool reports in the group of cases herein reported are of dependable value.

TABLE IV

Number of cases followed with frequent warm stool examinations for various periods after treatment\*

	6 Mos.	1 Yr.	1½ Yrs.	2 Yrs.	2½ Yrs.	3 Yrs.	3½ Yrs.
Number of Cases	53	11	6	10	6	3	10

\*55.8% of 104 cases were followed 6 months.  
44.2% of 104 cases were followed 1-3½ years.  
27.9% of 104 cases were followed 2-3½ years.  
Note: 97% of 104 cases remained ameba-free.

STATISTICAL END RESULTS OF COMBINED THERAPY

Using the combined method of drug therapy referred to above upon the representative group of 104 unselected cases of uncomplicated proven amebiasis, in 97%, or 101 cases, there was persistent absence of amebae from the stools after treatment. There was no unfavorable drug reaction in any of these 104 cases.

SUBSEQUENT TREATMENT AND RESULTS IN THREE CASES DEVELOPING RECURRENCE OF AMEBIASIS

The details of the treatment and subsequent results in these three cases, exhibiting recurrence of amebiasis after combined therapy, are outlined in Table V. In all three cases the recurrent infection was eradicated by the subsequent use of vioform. The practice of Reed and his associates has been followed in this clinic. This involves the routine administration of a second ten day course of vioform after a week's rest, and in the severe cases even a third or fourth course, after similar rest periods. The repeated course or courses, of such a relatively non-toxic drug, with only a week's intervening rest period, does not allow time

for an occasional remaining ameba to reinfect the colon.

Case I in Table V was a chronic relapsing type of amebiasis, with a long previous history of repeated exacerbations. For this reason she was given three courses of vioform. Case II, for unavoidable reasons, had received only three chiniofon retention enemata instead of the usual five treatments, and should possibly not have been included, therefore, in this group of patients treated by a uniform method of combined therapy. Case III illustrates a rare type of recurrence, the amebae reappearing one year after therapy, and after multiple negative examinations during the first six months. The amebae reappeared in this patient's stool after her summer vacation, and may represent reinfection rather than recurrence.

### SUMMARY

1. The most effective amebicidal drug now known fails in 10% of the cases to produce a permanent cure, when used alone as single drug therapy, and in a single course of treatment. There are disadvantages to any method which requires repeated courses of drug therapy. Therefore, a simple method of combined drug treatment which has reduced the therapeutic failures from 10% to 3%, with a single course of therapy, and which has produced no unfavorable drug reaction in 104 cases, seems worth reporting.

2. It has seemed important to review in detail the therapeutic effectiveness and the toxicity or lack of toxicity of each of the four outstanding amebicidal drugs.

3. The combined method of amebicidal drug therapy employed in treating this group of 104 cases consisted of administering by mouth a single course of carbarsone, consisting of 0.25 gram before breakfast and supper each day for ten days, and simultaneously giving 250 cc. of a 2.5% chiniofon ("Yatren") solution as a retention enema every other day during this ten day period, for a total of five treatments. These chiniofon enemata are given by a special technique, which is described.

4. The clinical material utilized consisted of an unselected group of 104 cases of uncomplicated amebiasis. (Two cases of acute amebic hepatitis and hepatic abscess were not included in this group since they received emetine). Upon the basis of differences in clinical manifestations, the 104 cases are divided into five sub-groups. (See Table I). As regards severity of infection, there is evidence that the cases of amebiasis treated in this clinic represent an average cross section of amebiasis, as seen in the temperate zone. In the tropical and subtropical zones it is recognized that infection with amebiasis tends to be more acute.

5. The warm stool and proctoscopic findings in the various clinical subgroups of cases are summarized in

Tables II and III. The method of collection and examination of warm stools is described.

6. The routine procedure of follow-up stool examinations, after amebicidal treatment in this clinic, has consisted of a careful warm stool examination by the same experienced parasitologist every week for four weeks after drug therapy, then every month for five months, and subsequently every six months for a total period of three years, or longer whenever possible. The period of follow-up stool study has varied from six months to 3½ years. The number of cases having various periods of follow-up stool examinations is specified in Table IV.

7. After using the above method of combined treatment, there was persistent absence of amebae from the stools in 97%, or 101 out of the 104 cases.

TABLE V

*Analysis of three cases presenting recurrence of amebae in stools after combined therapy (one course)*

	Clinical Type or Sub-Group	Time After Therapy Before Re-appearance of Amebae	Type of Subsequent Treatment Employed*	Result of Subsequent Treatment
Case I	Type II	24 days	Three courses of vioform	Stools still negative 2½ years afterward
Case II	Type IV	7 days	Single course of vioform	Stools still negative 9 months afterward
Case III	Type IV	Between 6 and 12 months†	Two courses of vioform	Stools still negative 20 months later

†Possible reinfection rather than recurrence.

\*Reed's method of administering vioform was followed, except that Case II should have received two courses.

8. There was no unfavorable drug reaction in any one of these 104 cases.

9. The three cases exhibiting a recurrence of amebiasis after combined drug therapy, received subsequent vioform treatment according to the method of Reed and his associates. (See Table V). The amebiasis was thus eradicated in each of these three cases.

10. In treating amebic hepatitis or abscess, in which carbarsone is contra-indicated, the combined treatment of choice consists of emetine hydrochloride hypodermically, in association with chiniofon orally and by retention enema, and surgery when indicated.

11. In conclusion, it is felt that the combined method of therapy administered to these 104 cases of uncomplicated amebiasis represents a safe and most effective method of treatment, which is superior to other methods thus far reported.

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## Gastrosopic Observations in Chronic Gastritis\*

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**M**ICROSCOPIC investigations of the mucous membrane of the stomach were attempted as early as 1854 by Jones Handfield (Manual of Pathologic Anatomy) and in 1858 by Wilson Fox (Transactions Medical Clinic), both of whom demonstrated inflammatory changes which they considered to be the expression of chronic gastritis. In 1880 W. Fenwick wrote on atrophy of the stomach in the nervous affections of the digestive organs, including pernicious anemia, and in 1886 Ewald showed atrophy of the gastric mucosa in pernicious anemia. But as early as 1833 and through 1838, Robert Carswell had already established the postmortem changes found in the gastro-intestinal tract, particularly the stomach, and these findings largely vitiated the latter above-noted observations.

In 1838 the observations of Beaumont were made on the living stomach. There must be care in interpreting Beaumont's descriptions; there is reason to believe that, because of alcoholism, indiscretions in diet, and the exposure of the stomach by the fistula, St. Martin's stomach was very likely the site of a chronic gastritis, subject to exacerbations.

In 1898 Faber and Bloch adopted the technique suggested by Damaschino (1880) and Chaffard (1882) and Hayem (1892-1897) of formalin instillation into the stomach and formalin injection into the peritoneal cavity immediately postmortem for the early and rapid fixation of tissue and consequent inhibition of postmortem change. The first investigations with this method were in pernicious anemia and other cases of achylia, in which various degrees of inflammatory changes were found usually with atrophy or adeny.

Then Konjetzny with Dalima, Paul and others examined resected stomachs from surgical cases (1923-24 and thereafter) and predicated a relationship between gastritis, ulcer and cancer. Finally Schindler in his Lehrbuch (1923) contributed the gastrosopic picture.

Bloch, Faber, Lange and Wintrup, Saltzman and Orator examined altogether about 30 formalized newborn stomachs in which no interstitial cell infiltration whatsoever was found, there being only a fine network of fibrillary threads supporting the gland structures, with perhaps a few lymphoid follicles. Occasionally the same findings were seen in older children and adults, but it is rare to find absolutely normal stomachs in adult material (Paschkis and Orator in Vienna came upon only 10 normal stomachs in an autopsy material of 9 months—several thousand cases, and

those only of fornix or corpus, the pyloric portion showing some change in all cases).

Acute gastritis is the result of direct irritation, usually chemical, or hematogenous infection with acute infectious diseases. Gastric mucosae of children dying of diphtheria show hemorrhage, erosion, edema, leukocytic infiltration and degeneration of glands. When these conditions heal, the regeneration of gland elements is by non-specific columnar epithelium with clear protoplasm, not the characteristic specific chief or parietal glandular cells. Some cases of influenza in adults show the same changes. Irritation gastritis was produced by alcohol in dogs, followed through the various stages to chronic condition (Ebstein, Popoff, etc.), which is usually atrophy or adeny and consequent achylia.

On the basis of his microscopic study of formalized sections, Faber divides *chronic gastritis* into chronic erosive gastritis localized in the antrum (not seen commonly as yet gastrosopically) and diffuse pan-gastritis leading to atrophy. Apparently, according to Faber (1), what we see as hypertrophic gastritis may be the regenerative processes, resulting in wartlike elevations due to proliferation of surface epithelium, replacement by non-specific columnar epithelium of the specific gland structures, and lymphocytic infiltration. In this view, the "hypertrophic" gastritis may be only a stage from superficial or acute gastritis to a final atrophic condition. In some cases this stage may be persistent: in other cases it may be only transient, or skipped entirely. This observation has not yet been confirmed by gastroscopy, although the transition from acute or superficial gastritis to atrophic gastritis is commonly seen.

The point of contention then between these histological observations, from either formalin or resected material, and gastrosopic findings seems to be concerned with the antrum gastritis or juxta-pyloric gastritis or gastro-duodenitis, and the so-called hypertrophic gastritis. On the one hand, the gastroscopist has so far seen very little of the antrum gastritis or juxta-pyloric or gastro-duodenitis described by the histologist; on the other hand, the histologist has apparently seen very little, if any, of the so-called hypertrophic gastritis described by the gastroscopist. Just where is the common ground, or the point of departure in this matter? Obviously there cannot be two different things seen by one group of observers and not by those using another method. Partial explanations are at hand.

Resection material is open to question because of the effect of trauma of handling and interference with circulation before removal. Gastrosopic observations may not be entirely accurate with respect to the antrum, because it is difficult to see; (in fact with the earlier rigid scopes, not seen at all in the majority of cases, and even with the flexible scope, not seen with

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the definition that regions of the body of the stomach are). One other point to be considered in evaluating the formalin fixed postmortem material studied by Faber et al is that the interstitial infiltrations and cellular replacement of gland structure may represent past experiences of the gastric mucosa. That is, they may be evidence that the gastric mucosa has been subject to inflammation, with consequent healing. All the stomachs in which these changes are found probably do not give rise to continuous symptoms. The more recent articles of Robertson (2) bear this out, in which he states that the *residual* lesions of ulcerative gastritis are the most frequent pathological changes seen in the stomach wall. These residual lesions are represented by collections of lymphocytes, irregular thickening and fibrosis of the muscularis mucosae, atrophy of the specialized gastric cells and more or less hyperplasia of the mucous glandular cells with varying degrees of disorganization of the mucous glands. But it is not likely that these changes seen microscopically are in every case responsible for continuous gastric distress; in other words, as Schindler (3) has suggested, "The positive findings of histology do not prove the existence of a clinical disease of the stomach." Another point is to be considered; inflammation of deeper tissues of the gastric wall, namely the submucosa and even the muscularis, may cause increased thickness of fold and rugae and produce the wide stiff rugae seen by relief technique roentgenographically, whereas the mucosa itself, covering this deep inflammatory condition may actually be atrophic as seen by the gastroscope (e.g. luetic linitis plastica). Just whether histologically or pathologically this is to be called hypertrophic or atrophic evidently depends upon whether one is speaking of the mucosa alone, or the total gastric wall.

From the gastroscopic standpoint, chronic gastritis is divided into 3 categories:

(1) *Chronic superficial gastritis*, characterized by edema, hyperemia, hemorrhage, exudate and erosions, and either healing or progressing to atrophy.

(2) *Chronic atrophic gastritis*, characterized by thinning of mucosa so that it appears grey, green or dirty white diffusely or in patches; where the underlying blood vessels are seen (never through the thickness of the normal mucosa) and associated (or not) with areas of superficial gastritis. The condition seen in the hypochromic, achylic, microcytic anemias is usually what may be called pure atrophy, without evidence of acute or recent inflammatory reaction (i.e. no edema, exudate, hemorrhage or erosion). The atrophic condition in pernicious anemia is often associated with evidence of more acute reaction (i.e. hemorrhagic spots and streaks, and occasional edematous areas, but in my experience, no erosion or exudate). In atrophic conditions the folds are thin and easily effaced by air pressure.

(3) *Chronic hypertrophic gastritis*, characterized by thick dull mucosa, often of warty, nodular, cobblestone, pebbled or mameloned appearance, with erosion, ulceration and hemorrhagic areas, but without exudate. The rugae or folds are thickened, more tortuous, do not efface upon dilating the stomach with air, and show in extreme cases beaded or serrated profile. The valleys between the folds are sometimes broader and at other times more narrow and show

elevations and irregularities, giving a pavement or mosaic design. It may be difficult in some cases to differentiate between true hypertrophy of the mucosa and unusually well visualized area gastricae of the normal mucosa. The normal mucosa may have the appearance of a pavement when it is particularly clean, or with certain degrees of inflation, in which case the rectangular areas of areae gastricae are marked off by thin crevasses and give a mosaic appearance. For true hypertrophy one must have actual elevation of these areas, usually also irregularity so as to produce a cobbled, pebbled or "etat mamelonné." Furthermore, as mentioned in discussion of postoperative gastritis, which is often "mixed," an appearance of hypertrophy may be given by a mucosa which is regenerating, in which case hyperplasia would be the more correct term. Some of these areas have been seen in certain cases of atrophic gastritis.

The gastric mucosa in the presence of a single, round peptic ulcer is either unchanged, normal or shows some congestive, edematous or hemorrhagic changes immediately around the ulcer. In cases of retention by chronic duodenal or gastric ulcer, superficial gastritis may be found. Occasionally I have seen very moderate, generalized, hypertrophic changes with duodenal ulcer, but never with gastric ulcer. I have never seen atrophic changes with either gastric or duodenal ulcer.

The changes in the mucosa of a stomach which has been subjected to operative measures are likely to be varied (4). In general, they are of the type of chronic superficial change with tendency to atrophy, but areas of hypertrophy are often seen. It may be that these stomachs show, in more rapid sequence, the changes which might be expected in other forms of gastritis. That is, the hypertrophic changes occur and are passed through rapidly from the acute superficial to the final atrophic condition, all stages being seen at a single observation because of the rapidity of progress. However, so far, in my experience and in that of most other gastroscopists, no change from a well established hypertrophic type of mucosa has been observed, either spontaneously or as the result of any therapeutic measures.

Eusterman (5) has recently remarked that the majority of cases of chronic gastritis are refractory to treatment, noting some gratifying "cures" in the chronic hypertrophic, erosive and ulcerative forms, and in some of the postoperative forms of gastritis; but treatment must be adequate and continuous at all times. Swalm and Morrison (6) found no evidence of change to normal or regeneration in atrophic gastritis, at least in those forms not associated with primary or secondary anemia. (The condition of achlorhydria following histamine injection has likewise remained constant). They think, however, that the hemorrhagic, erosive, ulcerative and edematous forms of gastritis can and do respond to treatment; in the case of superficial gastritis, irritative factors such as continuous drainage from a chronic sinus infection must be eliminated to prevent relapse and recurrence. The truly hypertrophic forms of gastritis persist. Symptoms may abate, but recurrence of symptoms is very common, and the condition itself is persistent. Mucosal changes become modified as in postoperative stomachs, but the

underlying change, whether it be hypertrophic or atrophic, persists once well established.

Schiff and Goodman (7) have had somewhat more favorable experience and they are more optimistic as to disappearance of what they have designated as superficial and hypertrophic changes. They even note a restoration to normal of the atrophic mucosa of pernicious anemia with liver, and that of hypochromic anemia with iron, and of primary atrophy with ventriculin. There may be some criticism of some of their cases, which seem to be of either short duration (three months: one week) or purely localized involvement. Also, some of the cases had shown the usual intermittency of history preceding the examination, and the presumption is that these might relapse again as they had already done, so many times. Schindler (8) thinks that the superficial forms may completely heal with treatment, not spontaneously; but if untreated, progress to a final atrophic condition which, once established, is permanent. The hypertrophic forms, in his opinion, never heal. However, he (9) has noted often a lack of correlation between the extent of the gastritis and the type, severity or frequency of distress in these patients. Gaither (10), in this connection, raises the question as to whether symptoms, or at least the severity of them, might depend more on the degree, location and extent of the lesion, rather than the actual type. Other gastroscopists have also noted the constancy of the changes in the mucosa, once established (Borland and others in discussion (11)).

There may be some support for the idea that atrophic gastritis is more resistant to treatment than other forms and more likely to exacerbations in the finding of Sebastianelli (12), who cultured the gastric secretions from 139 patients with gastritis and found:

- 74% positive cultures in atrophic,
- 50% positive cultures in hypertrophic,
- 35% positive cultures in superficial, and
- 46% positive cultures in gastro-duodenitic types of gastritis.

Conversely, the bactericidal power of the gastric juice was altered, unfavorably, in 91% of atrophic, 74% of hypertrophic or catarrhal, and 75% of gastro-duodenitic, and this alteration in bactericidal power antedated the appearance of positive cultures. There was no relation between type of bacterium and kind of gastritis.

Our own observation tend to confirm the majority of opinions quoted. We have many times seen hypertrophic or atrophic changes in the mucosa which seemed quiescent, in that there was no evidence at the time of examination of active inflammatory process such as hemorrhage, erosion or edema. Some of these patients had symptoms at the time and others had not. Most of them had had symptoms at some time, which was the reason for examination. We have also seen active changes in stomachs which were at the time causing the patient no symptoms. Perhaps the latent or quiescent conditions are comparable to those with the luetic stomachs, two of which we have seen with extensive nodular and scirrhous infiltration of the walls of the stomach, easily recognized gastroscopically and sufficient to produce a "leather bottle" effect on roentgen examination. These stomachs had given the patient absolutely no gastric distress at any time (13). It seems reasonable to suppose that these changes are permanent because of the usual long

duration of the clinical history, even though the symptoms may be periodic and intermittent. That healing of chronic gastric lesions does occur is instanced by the observations made in cases of gastric ulcer. The ulcers have been seen to heal, leaving a normal-looking gastric mucosa. At times, between episodes of activity of ulcer, we have seen submucosal hemorrhage in spots and watched these areas break down to form an erosion and later ulceration. Schindler (14) has described this process, and observations of Robertson (2) that the submucosal hemorrhage is a common gastric lesion are confirmatory. The exacerbation of activity in forms of generalized gastritis seems to be initiated by the same factors which bring about activity in ulcer; namely, nervous influences, fatigue, irritation from diet and infections.

The following cases, briefly summarized, indicate the irreversible changes seen in a few instances where opportunity for reexamination was given. It will be seen that although occasional improvement was evident, in all cases the fundamental change in the mucosa persisted. In contrast, a few cases of single round peptic ulcer are given.

Case 1. 3-6-36 — Hypertrophic gastritis — hemorrhagic ulcer. 5-20-36 — Granular mucosa. Ulcer healed but there is still hypertrophic change.

Case 2. 2-20-36, 4-4-36, 6-26-36 — Hypertrophic gastritis — changes persist all during this time; had history for 18 years. 11-6-36 — Hemorrhage.

Case 3. 2-28-36 — Ulcerative — hypertrophic. 7-8-36 — Ulcer healed, but still hypertrophic; granular mucosa.

Case 4. 5-13-36 — Hypertrophic gastritis — hemorrhagic, erosive. 5-29-36 — Improved, still hypertrophic change. 6-19-36 — Further improvement but hypertrophic type of mucosa still present. 3-17-37 — Same as original condition again — hemorrhage and erosions.

Case 5. 6-3-36 — Atrophic gastritis — edema and polypoid folds. 3-24-37 — Same condition. Thought to be allergic.

Case 6. 7-22-36 — Hypertrophic gastritis — hemorrhagic. 8-19-36 — Same. 9-23-36 — Worse — now ulcerated.

Case 7. 8-21-36 — Ulcerative gastritis — hemorrhagic. 10-2-36 — Partially healed. 10-30-36 — Ulcerated. 12-4-36 — Beginning atrophic changes.

Case 8. 4-1-36 — Hypertrophic, hemorrhage anterior wall. 6-26-36 — Ulcerated anterior wall. 7-29-36 — Healing. 9-23-36 — Healed but granular mucosa.

Case 9. 3-25-36 — Hypertrophic changes, hemorrhagic. Gastro-enterostomy — erosion at stoma. Hemorrhagic area anterior wall. 4-24-36 — Pigment spot at stoma — ulceration anterior wall.

Case 10. 3-12-37 — Hypertrophic. Ulceration and 4-23-37 — Hemorrhages. 5-19-37 — Hypertrophic, few hemorrhagic spots.

Case 11. 9-18-36 — Gastritis with erosion and hemorrhage. 11-18-36 — Gastritis with erosion and hemorrhage. 6-16-37 — Hemorrhagic streaks and linear erosion at angulus.

Case 12. 6-8-38 — Atrophic gastritis. 10-14-38 — Atrophic gastritis, more diffuse.

Case 13. 1-6-38 — Superficial gastritis. 10-7-38 — Superficial gastritis with atrophy.

*Examples of healed ulcer — no evidence of any other gastritis present:*

Case 1. 11-24-37 — Ulcer. 12-22-37 — Ulcer healing. 1-12-37 — Healed.

Case 2. 7-15-36 — Double ulcer. 8-12-36 — Healing. 9-16-36 — Healed.

Case 3. 7-10-36 — Pyloric ulcer. 7-31-36 — Healing. 8-28-36 — Healed.

Case 4. 3-11-36 — Hemorrhagic areas only. 4-17-36 — No hemorrhage. 6-24-36 — Normal.

Case 5. 5-13-36—Deep ulcer. 6-5-36—Healing. 7-3-36—Healing. 7-31-36—Healing but still small rather deep hold. Died of gastric hemorrhage in August, 1936.

Case 6. 4-3-36—Ulcer. 6-17-36—Healing. 10-26-36—Hemorrhagic spots. No ulcer.

The same persistence of the original conditions, once established, is seen in the atrophic mucosa of patients with pernicious anemia. Schindler (15) has more recently stated that he has seen regeneration and restitution to normal in 5 out of 23 cases examined. However, I have not seen such restoration to normal occur in any of the cases reexamined after treatment, although in some cases some evidence of regeneration was present. Fifteen cases were chosen, in which pernicious anemia had been disproved by all usual and accepted criteria. Six patients when reexamined showed still an atrophic mucosa, in two there was some improvement in that areas of regeneration were thought to be present. In one case the condition was definitely worse, i.e. the atrophy was more extensive. One patient had had inadequate treatment. One of the 15 was examined the first time when the blood was in good condition. Liver had been given in adequate form and dosage for four years but the gastric complaints had persisted. An actively atrophic condition was seen. One of the 15 had died, from what cause I do not know. Five of the 15 did not respond to my request for a follow-up study, and 2 of the 15 who did come in could not be reexamined because of acute upper respiratory infection. Another with marked mental changes was not reexamined, and in another, because of the complication of paralysis agitans, the examination was not repeated.

### SUMMARY

Of the 15 cases examined, 6 were reexamined, 1 was worse, 2 were improved, 3 were unchanged, 1 died, 5 failed to return and 3 could not be reexamined.

The article of Benedict, Jones and Hampton (16) is referred to frequently in the literature as giving proof that the atrophic condition of the mucosa in pernicious anemia may change as a result of treatment. A careful analysis of the cases presented therein does not substantiate that conclusion. Two of the 5 patients had carcinoma and were operated on, both of them *before* gastroscopic examinations were done. The other 3 patients had gastric polypi. One of these patients was not examined gastroscopically before operation. There is no mention, in the case of the four patients operated upon, of liver therapy following operation. So it would seem that these patients may not have had true pernicious anemia but malignancy or polypi with macrocytic anemia simulating pernicious anemia. Gastroscopic examinations were not done before treatment was instituted. Hence conclusions as to any change in the mucosa after treatment are impossible.

Cases of pernicious anemia summarized:

Case 1. 2-24-37—Atrophy. Hemoglobin 38%—RBC 1,700,000. 7-7-37—No change in the mucosa. Hemoglobin 82%—RBC 4,880,000. Improved. Therapy adequate.

Case 2. 3-3-37—Atrophy. Hemoglobin 56%—RBC 2,480,000. 5-10-39—Atrophy—slight effort at regeneration. Hemoglobin 88%. Improved. Therapy adequate.

Case 3. 5-4-38—Atrophy. Hemoglobin 83%—RBC 3,700,000. 5-27-38—Hemoglobin 77%—RBC 7,960,000. 6-15-39—No change. Improved. Therapy adequate.

Case 4. 1-18-36—Atrophy. Hemoglobin 52%—RBC 2,980,000. 6-22-39—Atrophy more marked. Hemoglobin 97%. Improved. Therapy probably not quite adequate.

Case 5. 5-1-36—Atrophy. Hemoglobin 70%—RBC 3,860,000. 4-26-39—No change. Hemoglobin 64%—RBC 3,080,000. Still some symptoms. Inadequate therapy.

Case 6. 2-3-37—Atrophy. Hemoglobin 53%—RBC 2,260,000. 4-5-39—Atrophy and areas of superficial gastritis. Hemoglobin 85%—RBC 4,760,000. Considered adequately controlled.

Case 7. 9-14-38—Atrophy with inflammatory change. Hemoglobin 93%. Not examined. Patient considered to have been adequately controlled for four years.

Case 8. 4-13-38—Diffuse atrophy. Single polyp of anterior wall of stomach. Not reexamined because of paralysis agitans and diabetes.

Case 9. 9-21-38—Diffuse atrophy. Hemoglobin 50%. (On 9-14-38 Hemoglobin 35%—RBC 2,040,000). Has had some liver but obviously inadequate amount.

Case 10. 5-27-36—Atrophy. Hemoglobin 42%—RBC 2,350,000. Untreated. Patient died in 1938, cause unknown.

Case 11. 11-4-36—Atrophy. Hemoglobin 76%—RBC 3,220,000. Untreated.

Case 12. 11-25-36—Atrophy. Hemoglobin 41%—RBC 1,900,000. Untreated.

Case 13. 12-2-36—Atrophy. Hemoglobin 40%—RBC 1,500,000. Untreated. Returned in 1939 but could not be reexamined because of acute upper respiratory infection.

Case 14. 2-3-37—Atrophy. Hemoglobin 38%—RBC 1,180,000. Untreated.

Case 15. 2-7-37—Atrophy. Hemoglobin 54%—RBC 1,680,000. Untreated. Not reexamined in 1939 because of marked mental changes and lack of coöperation consequent thereon.

### INCIDENCE OF VARIOUS DISEASES

The incidence of the several diagnoses made in my series of 700 gastroscopies is in approximate percentages as follows:

Negative findings—22.5%.

Unsatisfactory examination—0.75%.

Primary gastritis—44.0%—(Hypertrophic—22.5%, Atrophic—12.5%, Superficial—9.0%).

Carcinoma—10.0%—usually with gastritis.

Ulcer—7.0%—without general gastritis, occasionally local gastritis.

Postoperative—7.0%—mixed gastritis.

Duodenal ulcer—3.5%—occasional gastritis, hypertrophic type.

Pernicious anemia—3.0%—atrophic gastritis.

Polypi—2.0%—occasional gastritis.

Luetic stomach—0.25%—(linitis plastica type).

These figures agree remarkably well with those of Schindler (17) and Schiff and Goodman (7).

As for symptoms, I pointed out in a previous paper (14), superficial gastritis is likely to occur in younger people, with consequently a short history characterized by epigastric pain immediately on eating, usually not relieved by further food or self-medication and further characterized by episodic occurrence, often initiated by nervous strain, fatigue or infections. There may be anorexia, nausea and vomiting. In some of these cases the disease tends to merge into atrophic gastritis, and when well-established to give a history of persistent epigastric discomfort of a pressure type (at times relieved by eating or hot water drinking) with anorexia and nausea. The patients may also have sore mouth or tongue and complain during more acute exacerbations of substernal or subxyphoid pain. We

have reason to believe that diffuse atrophic gastritis may produce such general symptoms as fatigue, malaise and nervousness. In women particularly there may be anemia, and clinically the cases often present the so-called Plummer-Vinson syndrome.

The patients with hypertrophic gastritis complain of epigastric pain immediately after eating or after an interval. The pain may be relieved or aggravated by food or alcohol ingestion. There is nausea, and vomiting which often gives relief. In none of these types is there reference or radiation of pain, and night distress is uncommon. The tenderness, on physical examination, particularly palpation under the fluoroscope, is over the entire gastric area, occasionally localized to a point high up under the left costal margin, this latter finding being more common in superficial and superficial-atrophic gastritis. Occasionally the only symptoms the patient suffers are recurrent hemorrhages, without pain.

The results of analysis of gastric secretion after test meals is not very helpful, although in a general way the atrophic types tend to hypoacidity, anacidity or achylia. The symptom "burning" of the stomach seems to be of "functional" origin. Most of the patients with real gastric disease use some other descriptive term, whereas the psychoneurotic almost invariably calls his distress "burning." The allergists have thought that a burning distress in the abdomen accompanies some allergic disturbance of the gastrointestinal mucosa, but the idea is not so far proved by sufficient number of gastroscopies.

The pain is not localized in any of the types of gastritis but is diffuse over the gastric area, or, in superficial forms, located high in the left epigastrium at the costal margin. Tenderness is similarly located.

Vomiting is more common with gastritis than with ulcer.

Roentgen examination is helpful in that ulcer or cancer may be ruled out. The gastric area outlined by fluoroscopy may be diffusely tender. Occasionally, the irregularity or serration of the mucosal folds as seen in the silhouette may be suggestive. There is no close correlation, however, between roentgen findings and gastroscopic findings, although an occasional case has been correctly diagnosed as one of atrophic, edematous, hypertrophic, erosive or ulcerative gastritis.

Patients with the hypertrophic forms of gastritis have done best, when they did well at all, on an "ulcer" type of regimen, with the use of kaolin, colloidal aluminum hydroxide and calcium preparations. Some have improved symptomatically when given bile salts. Patients with the atrophic and superficial forms are harder to manage; in them bland diet, hot water with or without salt, given orally, and occasionally hydrochloric acid with meals have given results. We have so far not resorted to lavage, although we have used the carbonated alkaline waters by mouth. Vitamins are supplied in adequate amounts, especially B and C, either as food or by supplemental feeding of artificial or synthetic forms. Patients with hypochromic anemia and gastric atrophy are given iron and Vitamin B, and patients with pernicious anemia, liver in some form. We have not as yet used ventriculin consistently in cases of atrophic gastritis.

So far, although we have seen improvement of the more acute manifestations, such as ulceration, erosion, hemorrhagic areas, edema, we have not seen any permanent change in the fundamental mucosal disease, whether atrophic or hypertrophic.

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## Gastric Emptying Time and Acidity in Avitaminosis A in Dogs\*

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ONE of the earliest indications of Vitamin A deficiency is impairment of appetite. This anorexia has been attributed to the presence of ulcerative stomatitis or pharyngitis. The reviews of Robertson (1) and Bessey and Wolbach (2) present the pathology and physiology of Vitamin A but cite no evi-

dence of gastric function in Avitaminosis A. In the course of our studies upon the influence of Vitamin A on renal function (3) there was available a number of dogs in Avitaminosis A, for the determination of gastric emptying time.

### EXPERIMENTAL

All of the dogs except It. and P were 3 to 5 months of age when placed upon the deficient diet. The diets

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have been previously described (3). The test meal consisted of 10 gms. of the diet and 4 gms. of barium sulfate per kilo of body weight mixed with about 100 cc. of water. The details of technique were those used in earlier studies on gastric emptying (4). The gastric juice was collected by a stomach tube. The stomach was lavaged with water, 5 mg. of histamine was injected subcutaneously and the juice was aspirated. Its free and total acidity was determined in the usual way by titration.

### RESULTS

The normal gastric emptying time as determined by the X-ray method may be highly variable in any one animal. Many times the values check within 5 per cent but variations of 15 to 25 per cent are very common. In view of this normal variation, it was considered that the per cent change of emptying time in Avitaminosis A must be 25 per cent or more to be of

TABLE I  
*Average emptying time of the stomach*

Dog	Gastric Emptying Time			Severity of Avitaminosis A
	Normal	Avitaminosis A	Per Cent Change	
It	318 min.	441 min	+38	4
Fa	322	346	+7	1
	390	372	-5	1
Br	368	505	+36	1
T	393	448	-14	1
R	398	680	+71	1
		400	0	3
L	309	691	+124	4
Bl	331	376	+13	4
I	306	489	+34	1
II	335	310	-7	1
III	436	595	+36	4
IV	423	682	+61	1
P	469	603	+28	1
N	444	516	+16	3
Fu	301	411	+36	1
		342	-13	4
H	380	547	+44	1
		407	+6	4

significance. Ninety-four determinations of emptying time were made upon 15 dogs when normal and in varying degrees of Avitaminosis A. Dog Fa was subjected to two periods of Vitamin A deficiency.

Seven of the 15 dogs showed an increase in emptying time in Avitaminosis A of 28 to 124 per cent. In 3 other dogs, R, Fu and H, when anorexia first appeared the per cent increase in emptying time was 71, 36 and 44 respectively. However, within 4 weeks for dog R and 10 days for dogs Fu and H, the emptying time was within normal limits and remained so even though the signs of Vitamin A deficiency became progressively aggravated. The emptying time determined 3 days before terminus in dogs Fu and H was within normal range. Vitamin A was administered to dog R.

An attempt was made to grade the severity of the avitaminosis A in these animals on the following

basis: 1, greatly reduced food intake and some loss of weight; 2, those of 1 plus conjunctivitis and increased lacrimation; 3, corneal ulcer; 4, night blindness, greatly reduced activity, severe loss of weight. The severity of the avitaminosis A in these experiments is shown by the fact that only 8 dogs were able to survive even though Vitamin A administration had begun a few days before death.

As seen in the table, dogs It, L, I and III were classified as showing type 4 Avitaminosis A and their per cent increase in emptying time was 38, 124, 34 and 36 per cent respectively. On the other hand, dogs R, Fu and H showed a greater increase in emptying time when their avitaminosis was rated as 1 than when it was 4. Also dog IV had a 61 per cent increase in emptying time with a minimum of apparent avitaminosis.

In two dogs ulcers occurred in the mouth. Dog L developed a large ulcer at the base of the frenulum and had the greatest increase in emptying time. Dog F had a quarter size ulcer in the mucosa of the cheek, at which time the emptying time was within normal limits.

In only 7 of the 15 dogs was there a significant change in initial emptying time. Dogs P, IV and L showed a 3 to 9 fold increase during their Avitaminosis A but dogs III, II, I and It showed a 30 to 40 per cent decrease.

There was no significant change in either free or total acidity of the gastric juice or in its rate of secretion in Avitaminosis A as studied in the 4 dogs, It, Fa, T and Br.

### COMMENT

The anorexia which appears in Avitaminosis A in dogs is not due to ulcers in the mouth or pharynx because in only 2 of 15 dogs was there any ulceration. Furthermore, one of these dogs continued to eat a small quantity of food after the appearance of ulceration.

Gastric motility, as determined by emptying time, was found to be affected by Avitaminosis A in some animals. In 7 of 15 dogs, gastric emptying time was definitely increased. In some of the dogs (R, F and H) the emptying time was markedly lengthened with the initial appearance of anorexia. However, later it returned to normal values although the signs of Avitaminosis A were aggravated. The emptying time of dog III was markedly lengthened and the Avitaminosis A was of great severity. In spite of this, the dog continued to eat with some impairment of appetite. The variability of the results would indicate that impairment of gastric motility is not the cause of the anorexia in Vitamin A deficiency. It would seem more likely that the cause for the anorexia in Vitamin A deficiency is based upon some change in the central nervous system and not upon some change in the alimentary canal.

### SUMMARY

The free and total acidity of gastric juice and its rate of secretion in response to histamine was found to be about the same in 4 dogs during Avitaminosis A as under Vitamin A administration.

Final gastric emptying time in 7 of 15 dogs was increased 28 to 124 per cent in Avitaminosis A. In 3 other dogs it was increased 36 to 71 per cent at the initial appearance of anorexia but later emptying time



in these dogs was found to be within normal limits although the signs of Avitaminosis A had become progressively more severe. In the remaining 5 dogs gastric emptying time showed no significant deviation from the normal.

Anorexia in Avitaminosis A in these dogs was not due to ulceration of the buccal or pharyngeal mucosa because it occurred in only 2 of 15 dogs and one of these continued to eat. The variability of the results in the effect of Avitaminosis A upon gastric emptying

time makes it appear that the anorexia in this deficiency is due to changes in the central nervous system rather than in the alimentary tract.

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# The Precipitability of Pepsin by Colloidal Aluminum Hydroxide\*

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COLLOIDAL aluminum hydroxide, which was first introduced into gastro-enterological practice some fifteen years ago, seems now to be generally recognized as a valuable antacid in controlling gastric hyperacidity, especially in cases of peptic ulcer. In its favour it is to be particularly emphasized (1) that it is a strictly "nonsystemic" antacid (which rules out any possibility of the development of systemic alkalosis from its use, even if it is administered in very large doses), and (2) that it does not cause a "rebound secretion of acid" by the stomach (see Adams, 1939). It has been recently demonstrated in the dog (Komarov and Krueger, (1940)), that under certain conditions colloidal aluminum hydroxide, when introduced into the main stomach in sufficiently large doses, actually *inhibits* gastric secretion in a Pavlov-pouch in response to standard test meal, the volume of the secretion, its acidity and especially its peptic power being markedly decreased. It is noteworthy that all these effects were observed in an isolated part of the stomach which during the period when the experiments were carried out was never in contact with the aluminum hydroxide. In another set of experiments temporary local contact with colloidal aluminum hydroxide also produced a remarkable change in the gastric response to sham-feeding. The volume of secretion did not show any appreciable change—a decrease of acidity was noticeable for a short time only—but the peptic power of the secretion was markedly lowered and remained so for several hours in spite of the fact that no visible traces of aluminum hydroxide were present in the samples of gastric juice thus obtained. The latter observation and some other incidental observations suggested that colloidal aluminum hydroxide might possess a special affinity for the pepsin of the gastric juice, and prompted us to investigate this problem. The following is a report of a preliminary set of experiments, which, however, provided conclusive evidence that under certain conditions colloidal aluminum hydroxide does indeed precipitate pepsin of the gastric juice quantitatively and that from this precipitate pepsin

can be recovered also quantitatively in the presence of an excess of hydrochloric acid.

## EXPERIMENTAL METHODS

Two preparations of colloidal aluminum hydroxide were used, both kindly supplied to us by John Wyeth and Brother:

1. A standard commercial preparation known by the trade name "Amphojel."

2. A special preparation of pure colloidal aluminum hydroxide which in a dry form corresponds to the formula  $Al_2(OH)_6, Al_2(OH)_4, CO_2, 3\frac{1}{2}H_2O$ . The concentration of aluminum hydroxide in both preparations was about 6.0 per cent (equivalent to  $4.0 \pm 0.1$  per cent  $Al_2O_3$ ). As a source of pepsin, gastric juice from the Pavlov pouch of several dogs was used, either freshly collected or several days old, and either filtered or unfiltered. The peptic power was determined by Nirenstein and Schiff's modification of Mett's method (Hawk and Bergeim, 1937), the acidities by titration against Töpfer's reagent, methyl red and phenolphthalein as indicators. Further data on the experimental procedures used will be found below in the protocols of the experiments.

## RESULTS

In the first set of experiments the effect of Amphojel on peptic power was compared with that of sodium carbonate, when these substances were added to the gastric juice in quantities sufficient to buffer entirely the free hydrochloric acid in the gastric juice. The following are the results of one of these experiments, selected because the gastric juice used in that experiment had an exceptionally high peptic power (it was obtained from the Pavlov pouches of two dogs in response to a meal of bread). The original peptic power was 520 Mett units, the free and total acidities respectively 51 and 68 m.eq./l. In one test tube 1 cc. of Amphojel and 4 cc. of distilled water were thoroughly mixed with 5 cc. of gastric juice, with the result that a voluminous sticky precipitate was formed. In another, 2.6 cc. of 0.1 N sodium carbonate and 2.4 cc. of distilled water were mixed with 5 cc. of the same gastric juice; a small flocculent precipitate appeared immediately. The contents of the test tubes were

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stirred frequently during one hour at room temperature, centrifuged, and the supernatant liquid filtered. In the filtrate of the sample treated with Amphojel there was not a trace of peptic power left. This filtrate did not contain any free hydrochloric acid; it was negative to Töpfer's reagent and to Congo paper; the acidity, as titrated to methyl red, was 30 m.eq./l., and to phenolphthalein, 37 m.eq./l. The filtrate from the sample treated with sodium carbonate had a peptic power of 256 Mett units; it was also negative to Töpfer's reagent and to Congo paper; the acidity, as determined by titration to methyl red, was 5.6 m.eq./l., and to phenolphthalein, 15.6 m.eq./l. Thus in spite of its higher total acidity the Amphojel filtrate was entirely devoid of any peptic power, while the sodium carbonate filtrate retained about 50 per cent of its original peptic power. The experiment presented in Table I shows that very small quantities of 6 per cent colloidal suspension of aluminum hydroxide are sufficient to precipitate quantitatively all the pepsin from the previously neutralized gastric juice, and that all the pepsin thus precipitated can be quantitatively recovered from the precipitates by extraction with an excess of hydrochloric acid.

We studied also the effect of colloidal aluminum hydroxide alone, when mixed in varying quantities with acid gastric juice, in order to determine the possible relationship between the buffer action of colloidal aluminum hydroxide and its action as a precipitant of pepsin. All the experiments in this series gave virtually identical results when repeated with Amphojel or with a special preparation of colloidal aluminum hydroxide and with various kinds of gastric juice, such as juice freshly secreted or several days old, filtered or unfiltered. The accompanying graphs

(Figs. 1 and 2) serve to illustrate two types of experiments which we repeated several times, always with the same results.

The essential difference in the arrangement of such experiments was in the duration and temperature of incubation of the gastric juice with the colloidal aluminum hydroxide. As shown by the graphs, even very small quantities of alumina gel, which were far from sufficient to buffer all the free acidity of the gastric juice, were sufficient to precipitate considerable proportions of the pepsin originally present. The amount of pepsin thus precipitated was greater when the time of incubation was shorter and the temperature lower. This is evidenced in a striking manner by comparison of the action of 0.2 cc. of colloidal aluminum hydroxide on 5 cc. of gastric juice in the two experiments. In the experiment of June 7 (Fig. 1) 24 per cent of free hydrochloric acid was buffered and 26 per cent of pepsin precipitated in 15 minutes at 20° C., while in the experiment of June 20 (Fig. 2) 54 per cent of free hydrochloric acid was buffered and only 14 per cent of pepsin precipitated in 60 minutes at 38° C. The above quantity of colloidal aluminum hydroxide was close to 50 per cent of the amount sufficient to buffer all the free hydrochloric acid in the particular samples of gastric juice used. It will be seen from the graphs that quantities of alumina gel in excess of the quantities sufficient to buffer all the free acid, precipitate all the pepsin from the gastric juice entirely. These and other analogous experiments suggest strongly (1) that the action of colloidal aluminum hydroxide on the pepsin of the gastric juice is independent of its buffering action on hydrochloric acid, (2) that colloidal aluminum hydroxide has just as much affinity for the pepsin of the gastric juice as it has for the hydro-

TABLE I

*Precipitation of pepsin from neutralized gastric juice by Amphojel. Extraction of pepsin from the precipitates by hydrochloric acid*

Samples	Control	I	II	III	IV	V	VI
Volumes of Amphojel used (cc.)	0	0.1	0.2	0.3	0.4	0.5	1.0
Volumes of Precipitates obtained (cc.)	0	0.1	0.2	0.3	0.4	0.5	1.0
Analysis of the Filtrates							
Acidity (m.eq./l.)	Free	0	0	0	0	0	0
	Total	19	14	12	10	9	5
Peptic Power (Mett units)	61	0	0	0	0	0	0
Analysis of the HCl Extracts							
Acidity (m.eq./l.)	Free	—	66	64	65	75	50
	Total	—	78	86	100	101	108
Peptic Power (Mett units)	—	61	64	61	61	61	41

The gastric secretions from the Pavlov pouches of two dogs after a meal of bread and milk were combined and filtered. The peptic power of the juice was 61 Mett units, and the free and the total acidity 39 and 59 m.eq./l. respectively. 40 cc. of the juice were mixed with 15.6 cc. 0.1 N Na<sub>2</sub>CO<sub>3</sub> and 24.4 cc. H<sub>2</sub>O. Varying quantities of Amphojel (from 0.1 to 1.0 cc., as indicated in the first section of the table) were mixed with 10 cc. of the neutralized gastric juice. The samples were shaken for 5 minutes at room temperature and then centrifuged for 5 minutes at high speed. The supernatant fluid in each sample was decanted, filtered and analyzed (see second section of table). The precipitates were thoroughly drained and each extracted by stirring with 10 cc. 0.1 N HCl. To each sample some 0.1 N HCl was added (viz. 4, 8, 12, 16, 20 and 40 drops in consecutive samples from I to VI) in order to bring about complete solution of the precipitates. The precipitate from Sample VI was not entirely dissolved during 30 minutes at room temperature but in all the other samples solution was complete. The volumes of these extracts were brought to 51 cc. by the addition of distilled water. The extracts were filtered and analyzed (see third section of table). Pepsin determinations were made throughout in volumes of the filtrates and extracts equivalent to ½ cc. of the original acid gastric juice. Therefore all the values are directly comparable.

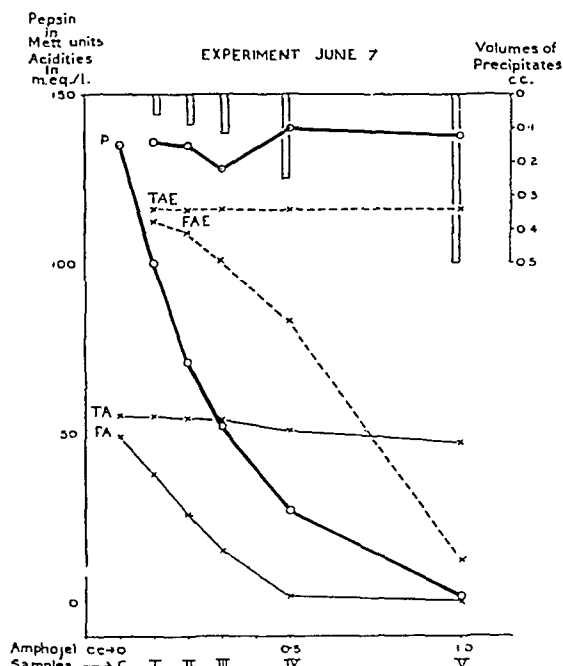


Fig. 1. Exp. June 7, 1939. The combined filtered gastric secretion from the Pavlov pouches of two dogs was used, after being preserved for 3 days at room temperature. Its peptic power was 135 Mett units, free acidity 97.6 and total acidity 110.4 m.eq./l. Amphojel in quantities of from 0.1 to 1.0 cc. was mixed with 5 cc. of the gastric juice and enough distilled water was added to each sample to bring the volume to 10 cc. The samples were shaken for 15 minutes at room temperature and then centrifuged for 5 minutes. The supernatant fluid from each sample was decanted, filtered and analyzed for pepsin and free and total acid. Enough 0.116 N HCl was added to the precipitates to bring the volumes to 10 cc. and the extraction was carried out in a water bath at 38° C. with frequent stirring for about 30 minutes until all the precipitates were dissolved. The extracts were then filtered and analyzed for peptic activity and acidities. (For explanation of signs, see Fig. 2).

chloric acid—perhaps even more, and (3) that while there is free hydrochloric acid (i.e. at pH < 4) the precipitation of pepsin is a reversible reaction. One other point must be emphasized. If small quantities of Amphojel are mixed with gastric juice, the pepsin is not merely absorbed by a suspension of colloidal aluminum hydroxide but an actual and very characteristic flocculent, protein-like precipitate appears as a result of chemical reaction. The precipitate rapidly settles down as a sticky mass which adheres firmly to the glass and which, after it has been centrifuged and separated from the supernatant fluid, is not very easily soluble in hydrochloric acid. Long-continued stirring and vigorous shaking are required in order to dissolve the precipitate completely, even if a considerable excess of hydrochloric acid is used. If solution is complete, the recovery of the originally present peptic activity is quantitative, as is illustrated in Fig. 1. However, if the precipitate is not completely dissolved, even though a large excess of hydrochloric acid is used, the recovery of pepsin from the precipitate is not complete (see Samples III and IV, Fig. 2).

While the above-reported data refer to the action of alumina gel on pepsin *in vitro*, the following obser-

vation made incidentally on a Pavlov-pouch dog illustrates that the reactions described above may take place also *in vivo*. On December 28, 1938, the pouch in one of the dogs was found to be full of blood (apparently as the result of mechanical damage and subsequent corrosion of a small artery by the gastric juice). It was decided to treat the pouch with Amphojel without changing the usual diet. After washing the pouch out with water we introduced 5 cc. of Amphojel into it (the pouch was able to retain up to 150 cc. of its own secretion day after day during half a year). Next morning there was very little blood in the secretion. Two further administrations of 5 cc. of Amphojel each were introduced into the pouch, on December 31 and January 1 respectively. The daily secretion from the pouch during this whole period was about 100 cc. per 24 hours. No blood was present in the secretion after December 31. During the next two

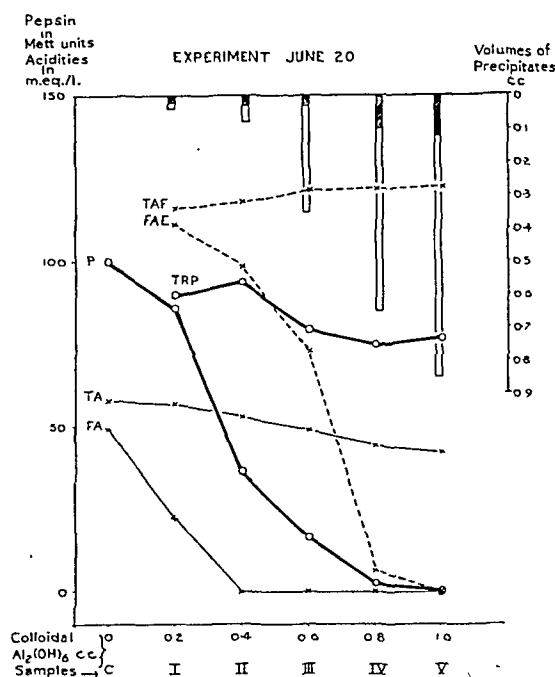


Fig. 2. Exp. June 20, 1939. Quite fresh filtered gastric juice from the same Pavlov-pouch dogs was used. Its peptic power was 100 Mett units, and free and total acidities 99 and 116 m.eq./l. respectively. Colloidal aluminum hydroxide (special preparation), in quantities of from 0.2 to 1.0 cc., was mixed with 5 cc. gastric juice and 5 cc. distilled water. The samples were shaken frequently and vigorously for about one hour at 38° C. The rest of the procedure was the same as in the experiment shown in Fig. 1. However, the precipitate was never completely dissolved in any of the samples by extraction with 10 cc. 0.116 N HCl.

"TA", total acidity, and "FA", free acidity of the filtrates. "TAE", total acidity, and "FAE", free acidity of the extracts. "P", peptic power of the filtrates. "TRP"—total recovered pepsin—is the sum of the values for peptic power of the filtrates and the extracts. Acidities are expressed in m.eq./l., peptic power in Mett units for 1 cc. of the original gastric juice or for the equivalent volumes of the filtrates or extracts.

Unshaded portion of columns show volumes of the precipitates which were subsequently dissolved by extraction with HCl. Shaded portions show volumes which remained undissolved.

days the secretion contained much of the characteristic precipitate in the form of large, sticky floculi. On January 3 the secretion appeared to be quite clear. On January 4 an experiment was performed in which the gastric secretion from the pouch in response to a standard test meal of 250 cc. of milk was studied. The hourly rates of secretion and the total secretion for 6 hours (12 cc.) were exactly the same as usually observed in experiments of that type. But very surprisingly there was no free hydrochloric acid in any of the 6 hourly samples and the peptic power in these samples was much lower than usual (viz. 0.8, 6.8, 17.6, 58, 58, 46 Mett units; the peptic power for the total 6 hours' secretion was 40 Mett units). For comparison we give here the corresponding data for the last experiment with milk, which was carried out one week before the treatment with Amphojel was started. The total secretion for 6 hours was 12 cc. The free hydrochloric acid in the samples ranged from 44 to 7 m.eq./l., being 33 m.eq. l. for the total secretion. The peptic power of the samples ranged from 470 to 70 Mett units, being 125 Mett units for the total secretion. It was a most surprising fact that greatly diminished peptic power and complete absence of free hydrochloric acid was observed in the secretion three days after the application of 5 cc. of Amphojel, notwithstanding that the pouch had been carefully drained at least four times a day for three days. This and other similar though less striking observations made on other pouch dogs suggest that Amphojel may act as a precipitant for pepsin also in the stomach and that precipitates thus formed, owing to their physical properties, tend to adhere firmly to the mucous membrane and that they resist to a great extent the solvent action of the hydrochloric acid of the gastric juice. Undoubtedly such precipitates carry down considerable quantities of unused colloidal aluminum hydroxide and for that reason continue to exercise an antacid and antipeptic action for a considerable time after the administration of aluminum gel.

#### DISCUSSION

The observations reported above would seem to be of interest to gastro-enterologists, since of all the commonly used antacids only colloidal aluminum hydroxide appears to have the property of precipitating pepsin, this in the presence of free hydrochloric acid being a reversible reaction. By precipitating the pepsin in inactive form, this substance is thus capable of depriving the gastric juice of some or all of its digestive power, depending on the quantities used. Of all the other antacids of clinical interest only synthetic magnesium trisilicate is reported to possess a somewhat similar property in being capable of adsorbing pepsin from acid solutions (Mutch, 1936). However, pepsin, once it is adsorbed by the silicate, is not released when the silicate is decomposed with acid. Hydrated silica ( $\text{SiO}_2 + \text{nH}_2\text{O}$ ), which is produced in the stomach by interaction with the hydrochloric acid of the gastric juice, is also capable of adsorbing pepsin. The silica residue after treatment with pepsin becomes activated and capable of digesting proteins. We believe that by proper use of colloidal aluminum

hydroxide in medical practice it is possible to adjust the peptic power of the gastric juice to any desired level, just as we have been able to do in many of our experimental animals. The regular administration of colloidal aluminum hydroxide by its introduction into the pouch in small quantities was found to be extremely helpful in this laboratory in post-operative treatment of Pavlov-pouch dogs. Severe ulcerations of the skin, which used to be quite common, disappeared almost entirely after the adoption of this treatment, so that it was possible to have the orifice of the pouches so well healed that the pouches retained large quantities of secretion. Since in our past experience such healing could not be achieved with other antacids and in fact could not be attained by any means whatsoever, we are inclined to ascribe the beneficial action of colloidal aluminum hydroxide on peptic skin ulcerations to the antipeptic property of this substance.

This report is to be considered as in the nature of a preliminary communication. Further studies on the precipitability of various constituents of gastric and pancreatic secretions by colloidal aluminum hydroxide are in progress in this laboratory.

#### SUMMARY

1. Colloidal aluminum hydroxide, when mixed *in vitro* with canine gastric juice in quantities sufficient to buffer its free hydrochloric acid completely, also removes quantitatively all the pepsin from the solution.
2. Complete removal of pepsin from gastric juice can be achieved with much smaller quantities of colloidal aluminum hydroxide if the free hydrochloric acid of the juice is buffered beforehand by sodium carbonate.
3. Colloidal aluminum hydroxide, when mixed with acid gastric juice in quantities smaller than those required for complete buffering of free hydrochloric acid in the juice, causes the formation of a characteristic protein-like precipitate, which carries down pepsin in quantities roughly proportional to the volumes of the precipitates.
4. Hydrochloric acid, in concentrations comparable with its concentrations in normal gastric juice, slowly dissolves the above precipitates and liberates pepsin. The recovery of pepsin under certain conditions is quantitative.
5. Observations on experimental animals prove that the above-described reactions can take place also *in vivo*; if colloidal aluminum hydroxide is introduced into the stomach, it exercises not only a pronounced "antacid" but also an "antipeptic" action, which may last for a considerable time after a single application.

Our thanks are due to Professor B. P. Babkin who supervised this work, and to John Wyeth & Brother, who furnished a supply of Amphojel.

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# The Effect of Aluminum Hydroxide Gel on Gastric Secretion in the Dog\*

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IT has been demonstrated by a great many investigators that colloidal aluminum hydroxide gel exhibits a considerable antacid action not only *in vitro* but *in vivo*. Thus, for example, Ivy, Terry, Fauley and Bradley (1937), on investigating two preparations, "Creamalin" (Cleveland Chemical Associates) and "Alucol" (Wander Co.) found that the reduction of the gastric acidities in 22 dogs during a 4-hour period following a test-meal averaged free HCl 20% and total HCl 6.5% in those receiving Creamalin, and free HCl 38% and total HCl 32% in those receiving Alucol. Emery and Rutherford (1938), who administered Creamalin to patients by the drip method for 24 hours, or orally every hour from 8 a.m. to 9 p.m., never found free acid present at any time during the day in the former case or at midnight in the case of the drip method. Adams, Einsel and Myers (1936) found that "prolonged ingestion of aluminum hydroxide cream led to a marked diminution of the gastric acidity." The same fact has been noted by other clinical investigators (e.g., Einsel, Adams and Myers, 1934; Woldman and Rowland, 1936; for literature, see Adams *et al.*, 1936, and Ivy *et al.*, 1937).

There is, however, another side to the question. Does aluminum hydroxide influence gastric secretion in some way, positively or negatively, or has it no effect whatever on the production and composition of the gastric juice? That aluminum hydroxide, unlike many other commonly used antacids, does not produce a "rebound" secretion of gastric juice is now generally admitted (Adams, 1939). However, there are indications that, after prolonged administration of aluminum hydroxide in large doses, there is a tendency on the part of the gastric glands to "compensate" the neutralizing effect of the drug. Thus Ivy *et al.* (1937) noted slightly higher acid values for the gastric contents after a plain test-meal in dogs treated with aluminum hydroxide. Emery and Rutherford (1938) reported that in humans, during 10 weeks' treatment with aluminum hydroxide, the secretory response to histamine gradually rose. Before treatment, histamine (0.5 mg.) elicited an average secretion of 98 cc. of gastric juice. By the end of 10 weeks the volume had gradually mounted to 120 cc.; the concentration of acid at this stage was lower than before the treatment with aluminum was begun, but the total output of HCl was almost at the normal level. On the other hand, Einsel, Adams and Myers (1934) found no difference in the response to histamine in patients before and after the application of aluminum hydroxide therapy.

As may be seen from the above review, the data concerning the stimulating effect of aluminum hydroxide on gastric secretion are not in agreement. More accu-

rate studies must be carried out both on animals and on man in order to determine what effect aluminum hydroxide has on gastric secretion after long continued administration, and especially whether it is really able to induce a hypersecretory state in the gastric glands or whether this effect, which was observed by some investigators, was due to some other factors. Unfortunately in many investigations, especially those performed on man, only the acidity of the gastric secretion has been determined and not the volume. Consideration of the acidity values alone, without taking into account other factors involved in the process of gastric secretion (volume of secretion, appetite, regurgitation of duodenal juices, etc.), may often lead to false conclusions regarding the secretory activity of the gastric glands.

We were interested in investigating how aluminum hydroxide affects the whole course of the gastric secretion, in respect of the volume and the composition of the juice, and the duration of the secretion (which is equivalent to the time of evacuation of the stomach). In the clinical literature we have not come across any definite indications concerning these important points. Adams, Einsel and Myers (1936), it is true, noticed that the gastric secretion provoked by histamine tended to decrease in patients subjected to aluminum hydroxide treatment. But several of their patients (perhaps the majority) had at the same time been placed on the Sippy diet (milk and cream, but no alkaline powders), and it is difficult to say whether the diminished response to histamine was due to the specific aluminum hydroxide therapy or to the general improvement in their condition.

## METHODS

In studying the problem of the effect of aluminum hydroxide gel on the process of gastric secretion, we carried out experiments on a dog with a Pavlov pouch and a gastric metal fistula, and a dog with esophagotomy and a gastric fistula. Aluminum hydroxide was introduced into the main stomach of the Pavlov-pouch dog, either alone or with food, and the secretion produced by the pouch in response to a standard meal was collected. In the dog with esophagotomy and a gastric fistula a certain amount of Amphojel (100 cc.) or the same amount of water in control experiments, was introduced into the stomach before sham-feeding and kept there for 30 minutes, after which time the stomach was drained, and the response to sham-feeding under strictly controlled conditions was then determined.

The preparation of aluminum hydroxide which we used was a commercial one, John Wyeth and Brother's "Amphojel," with which the firm kindly supplied us. Concerning the composition of Amphojel, the company

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states as follows: Amphojel consists of freshly precipitated aluminum hydroxide in the form of a colloidal gel, containing aluminum hydroxide (6.1%), a trace of carbonate (in the form of a complex aluminum carbonate—approximately 0.001%), a trace of chloride (approximately 0.15%). Alumina gel is amphoteric. With a pH of 6.8 it is capable of neutralizing (to Töpfer's indicator) at least 12 times its volume of N/10 HCl.

Aluminum hydroxide combines with free HCl in the stomach to form aluminum chloride. In the presence of the alkaline secretions of the intestine the aluminum hydroxide is presumably re-precipitated by the hydroxyl ions of the intestinal juices, forming sodium chloride as another product of reaction. However, no actual investigation of the problem of the transformation of aluminum chloride into aluminum hydroxide *in vivo* has been carried out, as far as we know. It is said that aluminum hydroxide is not absorbed in the intestine.

### EXPERIMENTAL RESULTS

#### (1) *Experiments on Pavlov-pouch dog*

The following types of experiments were performed on the Pavlov-pouch dog:

I. Amphojel in various doses was administered to the dog through the fistula at the same time as a meal of meat was given by mouth.

II. One feeding of meat, during which the animal received Amphojel, was given, followed by a second feeding of meat 4 hours later.

III. Amphojel was given first and meat afterwards.

In each set of experiments, control tests were carried out, in which, instead of Amphojel, corresponding amounts of water were given.

I. The animal was kept on a standard diet, deviations from which were always noted. Amphojel was administered through the gastric fistula in various doses just as the dog finished eating a meal of meat. A dose of 20 or 40 cc. of Amphojel never produced any noticeable effect. When 60 cc. of Amphojel was given, it was observed in some of the experiments that there was an inhibition of the gastric secretion of the pouch, the volume and the free and total acidities and peptic power of the juice being diminished. In other experiments there was no marked reduction in the volume of the secretion nor depression of the acidities, but the peptic power was markedly lowered. We are inclined to think that variations in the results of the 60 cc. dose, administered simultaneously with the meal, were due to uneven distribution of the aluminum gel over the walls of the stomach and perhaps of the duodenum.

Although the results of this series of experiments were far from conclusive, they provided certain important indications:

1. Under certain circumstances Amphojel inhibits the production of gastric juice, as shown by the decrease in the secretion of the pouch notwithstanding that the substance does not come in contact with the secreting surface of the isolated pouch.

2. When given in large doses such as 60 cc., Amphojel lowers the free and the total acidity and the peptic power of the pouch juice. The effect on the acidity is probably due to the diminished rate of gastric secretion; that on the peptic power is to be attributed to some unknown action of Amphojel.

3. Even though the volume of the gastric secretion is not reduced under Amphojel administration (60 cc.), the peptic power of the juice is nevertheless diminished.

4. It was observed that, when the usual meal was given after an experiment in which Amphojel had been administered with food, a smaller secretion was obtained than after a control experiment.

II. A fresh series of experiments was planned, in order to study the late effect, or rather the after-effect, of Amphojel. For this purpose the dog was fed

TABLE I

Pavlov-pouch	Volume (cc.) in 6 hrs.	Acidity (m.eq./l.)		Pepsin (Mett Units)	
		Free	Total	Concentration	Output
Average for 3 experiments with water	28.6	113.0	132.7	136.7	4016.0
Average for 3 experiments with Amphojel	16.9	108.5	128.0	68.0	1346.6

twice with 200 gm. of raw meat, the second feeding taking place 4 hours after the first. In this series a larger total dose of Amphojel (or of water in the control experiments) was given, 90 cc. being administered in three doses of 30 cc. each, through the fistula immediately after, 1½ hours and 2½ hours after the first feeding.

Fig. 1 shows the results of two representative experiments, selected from a large number of analogous experiments; in one case, the control, water was administered, and in the other Amphojel. From these experiments it is evident that not only was the volume of the gastric secretion from the pouch reduced after Amphojel, especially after the second feeding (con-

TABLE II

Sham-feeding	Volume (cc.) in 2 hrs.	Acidity (m.eq./l.)		Pepsin (Mett Units)	
		Free	Total	Concentration	Output
Average for 3 experiments with water	101.5	133.4	139.9	172.4	17822
Average for 3 experiments with Amphojel	91.6	111.7	135.1	63.1	5939

sisting of meat alone), but there was some reduction in the acidities and a very marked fall in the peptic power of the juice, again especially pronounced after the second feeding. These experiments show that a certain time is required for the full inhibitory effect of Amphojel to develop. It seems that the inhibitory effect of Amphojel lasts for a considerable time. We often observed that even two days after the administration of Amphojel the volume of the secretion (evoked by a standard meal) had not returned to the normal level. However, since the data concerning the "after-effect" of Amphojel are incidental observations

only, the problem must be investigated separately before this fact can be regarded as fully established.

III. All the above-reported experiments showed that the inhibitory effect of Amphojel only developed gradually. Therefore another form of experiment was adopted. 35 cc. of Amphojel, or of water in control experiments, was introduced into the empty stomach three times at intervals of half an hour. To ensure that the Amphojel would be evenly distributed over the surface of the stomach, the dog was laid on its back and rolled from side to side. Then meat (200 gm.) was fed to the animal half an hour after the last administration of Amphojel or water. The results are shown in Fig. 2 and Table I. Fig. 2 shows two representative experiments and Table I total and average figures for all the experiments of this kind. From Fig. 2 it may be seen that Amphojel by itself produced a somewhat larger volume of secretion from the pouch than water alone, namely 4.9 cc. as compared with 3.8 cc., but the peptic power of the Amphojel secretion was much less. Thus, for example, in the last half hour the secretion on water (1.5 cc.) was practi-

cally equal to that on Amphojel (1.6 cc.). However, the total output of pepsin in the former was 624 ferment units, while in the latter it was only 200 ferment units, i.e., only about one-third.

Fig. 2 and Table I also show that after Amphojel the gastric secretion on meat is diminished in volume as well as in peptic power and acidity. These facts are the more remarkable in that the Amphojel naturally never came into contact with the mucous membrane of the pouch.

Fig. 3 illustrates (a) a control experiment in which meat was fed to a Pavlov-pouch dog and (b) an experiment where the same amount of meat was given after Amphojel had been introduced into the main stomach. 20 cc. of Amphojel was introduced into the main stomach through the metal fistula 15 minutes before feeding with meat, and another 20 cc. of Amphojel was given 2 hours after the first. Although the amounts of Amphojel administered in this experiment, which was selected from a number of analogous experiments, were relatively small, there was a striking difference in the response of the pouch

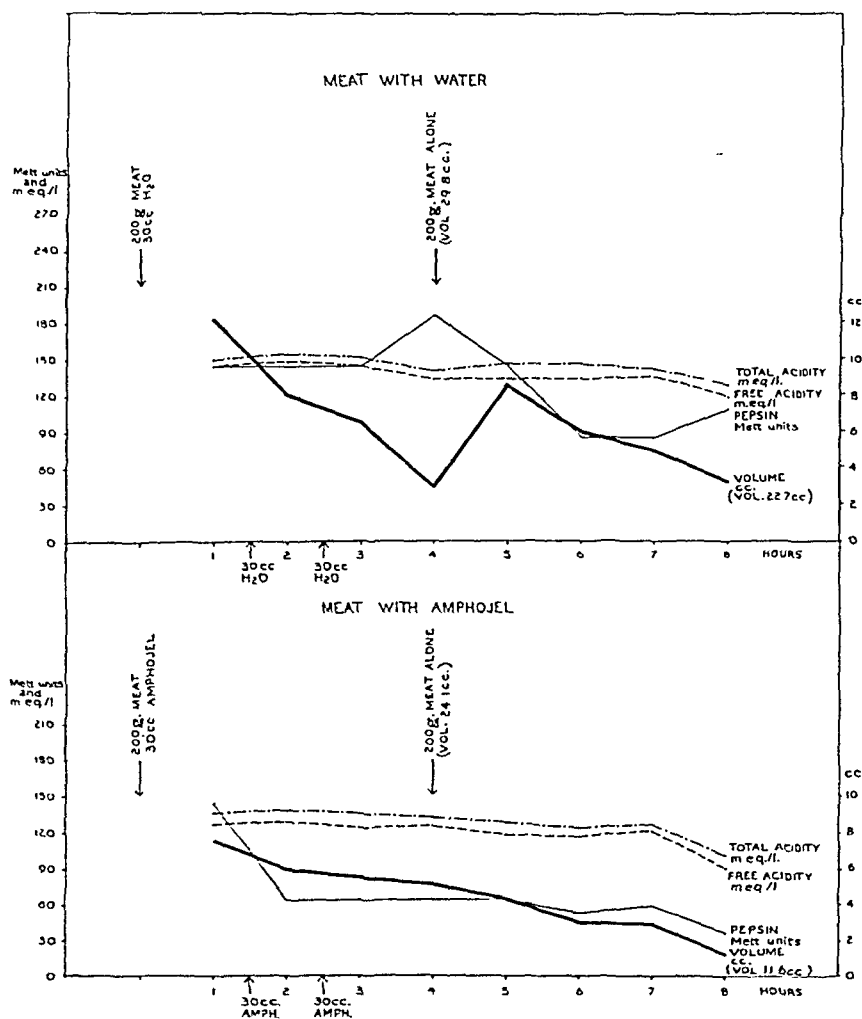


Fig. 1

mucosa to ingestion of meat in respect of the volume of the secretion and the peptic power as compared with the control experiment. There was hardly any difference in the acidity of the gastric juice in the two cases.

(2) *Experiments on dog with esophagotomy and a gastric fistula*

In this animal we studied the direct effect which the introduction of Amphojel into the stomach produced on gastric secretion provoked by sham-feeding with meat. 100 cc. of Amphojel, or of water in control experiments, was introduced into the stomach through the fistula and kept there for 30 minutes, after which time the fistula was opened and the residue (about 50 to 60 cc. in the case of Amphojel) was allowed to run off. 15 minutes later a 5-minute sham-feeding with

meat was performed. In the control experiments not more than a few cc. of water, if any, was usually found in the stomach after a period of 30 minutes.

The experiments gave very uniform results. The volume of gastric secretion was not affected by Amphojel and varied as usual within reasonable limits from day to day. Therefore the diminished secretion of gastric juice after Amphojel administration in other experiments could not be explained by loss of appetite in the animal. At any rate the dog ate the meat during sham-feeding just as eagerly as ever. In the Amphojel experiments the total acidity was very low in the first 15 minutes, when the gastric juice was turbid from admixture with Amphojel, but during the next half hour, when the juice became clear, its acidity reached approximately the same values as in the con-

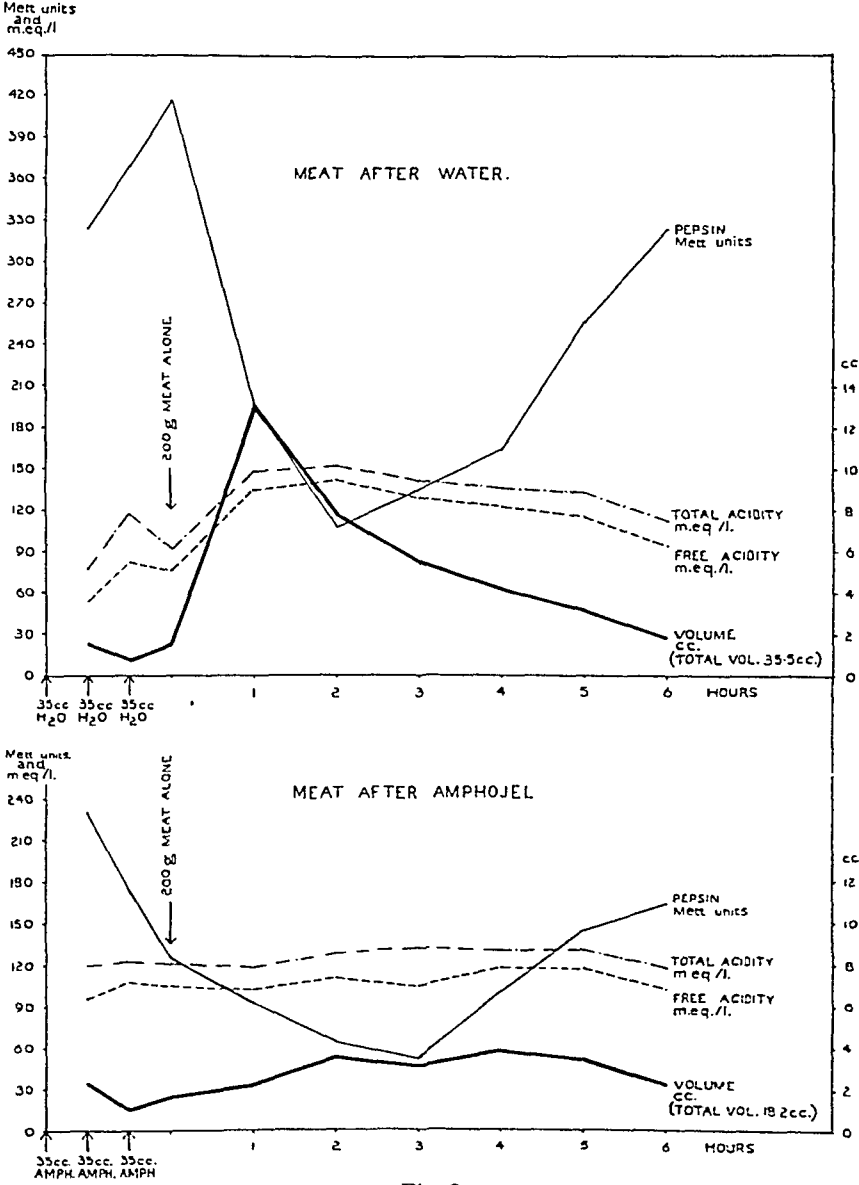


Fig. 2



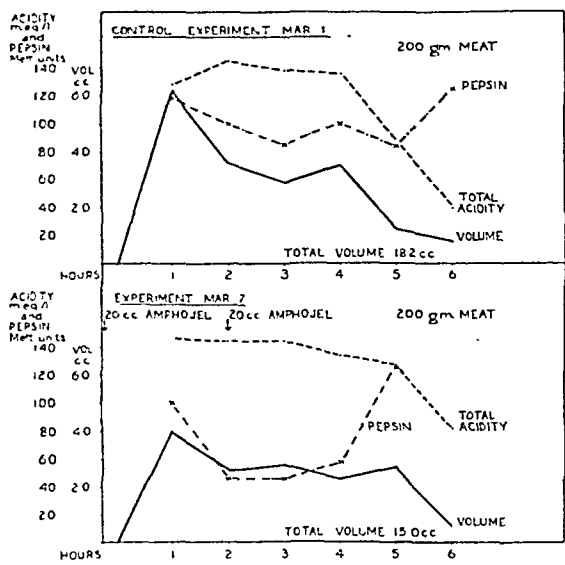


Fig. 3

trol experiments. The free acidity of the juice after sham-feeding was extremely low in the first quarter hour, falling in some cases to zero or a few milliequivalents per litre, but by the end of the second quarter hour it had returned almost, though not quite, to the normal high level. The most striking difference between the control experiments and those with Amphojel, however, was observed in the concentration of pepsin. After Amphojel, although the gastric juice which was let out from the stomach in the latter period of the secretion seemed to be clear and without any turbidity, its peptic power was greatly diminished throughout the experiment. Fig. 4 shows two examples selected from a series of analogous experiments, in which the above-described relations are clearly seen. Table II contains average data from three other control experiments with water and three experiments with Amphojel, confirming what has been said above.

The conclusion which may be drawn from this series of experiments is that Amphojel which has been introduced into the stomach and partly discharged into the duodenum does not diminish the volume of gastric juice in the nervous phase of the secretion. The acidity of the juice was lowered only for a short period of time, during which the Amphojel was presumably admitted to the juice in greater amount, but the peptic power suffered a great diminution throughout the whole secretory period.

DISCUSSION

It is not yet clear how aluminum hydroxide which has been introduced into the main stomach affects the process of gastric secretion in an isolated gastric pouch. However, we have obtained some indications concerning its mode of action.

(1) *Diminution of the volume of secretion.* Since the acidity of the gastric contents is lowered by aluminum hydroxide, and hence the inhibitory reflex produced on gastric secretion by acid from the duodenum (Day and Webster, 1935) is weakened, one would expect that after the administration of aluminum hydroxide the secretion would be increased. As a

matter of fact the result is the reverse—there is a diminution of the secretion, and this might be explained in several different ways.

(a) Aluminum gel adsorbs not only acid but probably also some of the chemical stimulants that are contained in meat or are formed from it in the course of gastric and intestinal digestion. Perhaps they are not released from the aluminum gel in the intestine and therefore the extent of their absorption is diminished. These substances might include, for example, some of the nitrogenous bases which possess a powerful retagogue effect.

(b) We observed that Amphojel, on coming in contact with the gastric mucus, forms a sticky mass which adheres tenaciously to the mucous membrane. In certain cases, for medicinal purposes, Amphojel was introduced into the stomach pouch in different dogs. It took two to three days to wash it out completely from the pouch. During this time the gastric juice flowing from the pouch possessed a diminished acidity. We used Amphojel also to cure the erosions and ulcers which often formed around the orifice of the pouch. In one case when, presumably as a result of mechanical irritation, bleeding began from the pouch, it was soon

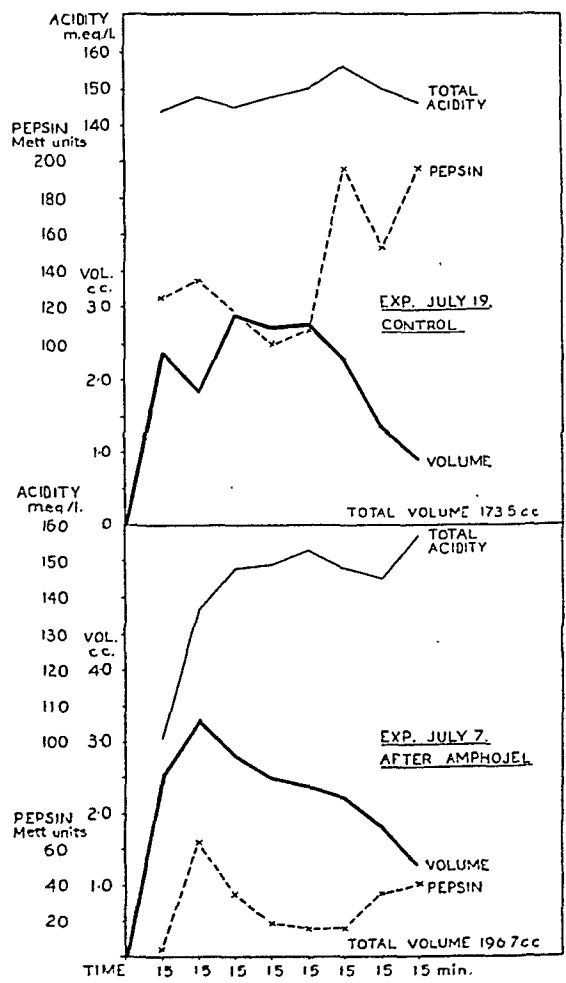


Fig. 4

arrested by injection of Amphojel into the pouch. According to Kyger, Hashinger and Wilhelmj (1939), aluminum hydroxide is highly effective in controlling severe hemorrhage in ulcer cases. Ivy, Terry, Fauley and Bradley (1937) also observed that aluminum gel combines with mucus to form a sticky paste, which coats the mucosa of the stomach and duodenum. This coating of the mucous membrane will undoubtedly interfere with the absorption of various substances, at least in the duodenum and upper part of the small intestine, as well as with the formation of gastrin in the pyloric part of the stomach. It may be seen from the work of Beazell, Schmidt and Ivy (1938) that, although the total weight of the feces of dogs receiving an aluminum preparation was increased owing to greater content of water, the absorption of nitrogenous substances and fat was not markedly affected. Therefore in the lower part of the gastro-intestinal tract the deficiency in absorption is presumably compensated. According to Adams, Einsel and Myers (1936) aluminum is not absorbed from the intestine; in man there is no disturbance of the mineral metabolism, no hypochloremia and no change in the total base or in the alkaline reserve of the plasma ( $\text{CO}_2$  capacity).

(2) *Reduction of acidity.* This is probably a secondary phenomenon due to the diminished volume of juice secreted by the pouch, and perhaps to the somewhat increased discharge of mucus by it, when Amphojel has been introduced into the main stomach.

(3) *Lowering of the peptic power.* We are inclined to attribute this to diminished absorption by the pyloric and duodenal mucosa of some chemical stimulants which normally increase the discharge of pepsin from the peptic cells. Among such substances are, for example, choline and lecithin. In this laboratory MacIntosh and Krueger (1938) have demonstrated that administration of choline or lecithin increases the response of the gastric glands to a standard test-meal (meat or butter).

The local effect of Amphojel on gastric secretion, as exhibited in the experiments where Amphojel was introduced into the stomach of a dog with esophagotomy and a gastric fistula, is manifested chiefly in a

marked lowering of the peptic power of the gastric secretion. This was observed for several hours after the Amphojel was let out of the stomach but also after the gastric mucosa was thoroughly washed by a rapid flow of gastric juice. It was observed that Amphojel forms a highly viscous and sticky precipitate with the proteins of the gastric juice, and especially with mucus. Apparently a film of such a precipitate is formed over the whole of the gastric mucosa, in which some of the alumina gel is included. The short contact of the gastric juice with this presumably very thin film did not markedly affect the acidity of the secretion but it was sufficient to reduce its peptic power greatly. This remarkable effect of Amphojel on pepsin in the gastric juice is being further investigated in this laboratory.

## CONCLUSIONS

The above-reported experiments on dogs must be regarded as of a preliminary nature. However, they establish certain facts, viz.:

(1) Aluminum hydroxide, when introduced into the stomach, influences the secretion of gastric juice in a part of the gastric mucosa separated from the main stomach and forming a pouch. In other words, it acts *par distance*.

(2) Such an application produces a greater effect when given some time before a meal.

(3) It has no harmful effect on the animal, even when administered in large doses. No general symptoms of poisoning nor any local unfavorable effects, such as constipation or vomiting for example, were ever observed in our animals.

(4) Aluminum, unlike the alkalis, produces as an after-effect an inhibition of gastric secretion rather than an increase.

(5) The peptic power of the gastric juice is greatly diminished not only when the juice comes into direct contact with Amphojel in the stomach, but also in the case of the secretion of the separate Pavlov-pouch when Amphojel is introduced into the main stomach.

Our thanks are due to Professor B. P. Babkin, who supervised this work, and to John Wyeth & Brother, who furnished a supply of Amphojel.

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## Pseudo-Surgical Syndromes Produced by Salmonella Organisms

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**H**UMAN infection by the *Salmonella* group of bacteria is of interest primarily as an epidemiological problem. Fairly numerous outbreaks, epidemic in nature, have been reported in various parts of the world, especially in the recent period since the World War.

The sporadic case is of importance to the surgeon because this type of infection occasionally simulates the clinical picture of the acute intra-abdominal surgical infection so closely that surgical intervention may be advised and carried out on the basis of a mistaken diagnosis. If the true nature of this type of case is not recognized and corroborated by proper bacteriological studies, it is quite easy to realize how such an individual may become a source of infection with resulting outbreak of the disease on a scale of epidemic proportions. For these reasons the authors feel that the following cases should be reported.

Case 1. A. C., No. 113116, a 26 year old white male, was admitted to Beth Israel Hospital on July 8, 1939. Family and past history are irrelevant to his present condition. His illness began suddenly twelve hours before admission with severe generalized abdominal pains, most marked in the paraumbilical region. He vomited several times during the night and had several loose bowel movements. There was no pus or blood in his feces, and seven hours after the onset of this pain the patient had a marked shaking chill.

On physical examination the patient appeared acutely ill. His temperature was 103, pulse 120, respirations 26. With the exception of the abdominal findings, the physical examination revealed no abnormalities. The abdomen was distended and the musculature over its lower half was slightly spastic. No masses could be felt. There was definite tenderness, and rebound tenderness over the lower abdomen.

The impression obtained was that the patient was suffering from acute appendicitis. His white blood count was 15,900 with 91% polys, 12 staffs. Blood culture was negative. On July 11 a laparotomy was performed. The peritoneal cavity contained a moderate amount of free clear yellow serous fluid. The serosa over part of the ileum showed a moderate inflammatory reaction. The appendix proper showed no evidence of inflammation on gross and on microscopic examination. The post-operative course was uneventful. The temperature came down by lysis. Bacteriological examination of the feces obtained after operation (7-12-39) was positive for bacteria of the *Salmonella* group.

Comment: This patient was operated upon for appendicitis, a condition that was not found at operation, and the true nature of the disease was discovered when the bacteriological examination of the stool revealed the *Salmonella* organism.

Bacteriological and serological findings: Stool culture on 7-12-39 *Salmonella typhi murium* (other names: *Bacillus aertrycke*, *Bacillus pestis caviae*). Blood culture of 7-13-39 sterile. Serum agglutinins for *Salmonella typhi murium*: 7-12-39, 1:50 negative; 7-17-39, 1:400 positive; 7-20-39, 1:1600 positive. The serum of 7-20-39 was analyzed for the presence of antibodies corresponding to the various antigens of *S. typhi murium*. *S. typhi murium* is a diphasic organism composed of a somatic or O-antigen, and of two flagellar antigens, the so-called specific and the non-specific H-antigens. The serum contained antibodies for all three antigens, the strongest reaction was obtained with the specific H-antigen (1:1600).

Cultures representing other types of the *Salmonella* group were agglutinated by the patient's serum corresponding to their antigenic composition, i.e., they gave positive reactions as far as they shared antigens with *S. typhi murium*. Since the O-antigen as well as the non-specific H-antigen are widely distributed within the group, positive reactions with many *Salmonella* types were obtained.

Case 2. B. R., No. 113033, a 55 year old white female, was admitted to Beth Israel Hospital on July 8, 1939, with history of abdominal pain and fever of 24 hours duration. Sudden onset the day before admission with severe epigastric burning followed shortly by cramp-like periumbilical and R.L.Q. pain. Accompanying the onset of this pain was a chill with temperature of 103 degrees. The above pain persisted until admission. In addition there was occasional slight pain in the R.L.Q. Past history revealed moderate intolerance to fatty foods, for the past three years, and an episode two months ago of rather severe R.U.Q. pain. There was no previous history of jaundice, clay-colored stools, etc., no definite dietary indiscretion, and no obvious history of ingesting contaminated food. Patient's husband is a butcher but she handles no food other than that in the household. Patient vomited four times on the day of admission.

Physical Examination: Temperature 102.4, pulse 124, respirations 28, blood pressure 138/82. An obese white female, appearing acutely ill, perspiring profusely, not dyspneic, orthopneic, or cyanotic. Heart and lungs negative. The abdomen was slightly distended with marked tenderness on the right side, chiefly in the upper two-thirds and in the right flank. No mass palpable. Pelvic examination negative. The extremities revealed varicosities of both legs.

Laboratory Data: Urine essentially negative. RBC. 3.27 million, 78% Hb., 18,000 WBC., 93% polys, 11 staffs. Icteric index 9.2. Blood culture negative. Electrocardiogram was within normal variations.

Course: Patient's temperature ranged between 102 and 103 for the first five days of her hospital stay. After the first two or three days abdominal signs became less marked and more localized in the right upper quadrant. However, the patient developed fairly

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rapid respirations with dullness, diminished breath sounds, and rales at both bases, posteriorly, so that a clinical diagnosis of broncho-pneumonia was made. Portable X-ray of the chest showed a high position of both diaphragms with impaired aeration at the left base, suggestive of fluid. Sulfapyridine therapy was instituted. A day later temperature returned to normal and stayed normal for five days. At this time, although there were still rales at both bases, because of nausea and vomiting, and five days of normal temperature, administration of sulfapyridine was stopped. Following this, the temperature ranged between 99.5 and 101, and the patient complained of diffuse abdominal pains for the next week. On the third hospital day, while temperature was still 102, the blood count had dropped from its original 18,000 WBC. to 3,050. Because of this, and the abdominal cramps, a typhoid or paratyphoid infection was considered, and a stool culture and blood for Widal and Paravidal was taken, as well as blood culture. Results of these tests obtained several days later, after sulfapyridine had controlled patient's temperature, revealed a *Salmonella* organism of the Paratyphoid C group. On the 18th hospital day, patient felt chilly and temperature rose abruptly to 103. She appeared somewhat icteric and the icteric index had risen from 7, two days previously, to 16.9 on the day of fever. The white count, which had been 4,860, rose abruptly to 22,000 with 84% polys and 6 staffs, and there was definite tenderness in the R.U.Q. Temperature slowly dropped to within 1 or 2 degrees of normal, and continued fluctuating between 99.5 and 102 for the next two weeks. The marked tenderness in the R.U.Q. and the leucocytosis, however, only persisted one or two days following the acute episode. It was felt that this was an acute exacerbation of a chronic cholecystitis. Duodenal drainage performed several days later revealed the same organism (Paratyphoid C group) in the B bile. It was felt that the entire episode from the time of admission to the hospital might be explained on a basis of food poisoning infection with the *Salmonella* organism of the Paratyphoid C group, with infection of the gall bladder as well as of the intestine. In view of the absence of cough, sputum, and the typical sign of consolidation, it was impossible to say that the pulmonary episode which apparently responded to sulfapyridine was definitely a pneumonia. Patient's stool continued on many repeated occasions to show the above organisms and it was decided to isolate the patient until two negative stools were obtained at 48 hour intervals.

Comment: This patient was prepared for operation in the surgical ward with the diagnosis of acute cholecystitis or acute appendicitis (high lying appendix), but, owing to the development of an apparent bronchopneumonia, was transferred to the medical ward for treatment. Here in the usual course of events, investigation revealed the true nature of the patient's illness, and no surgical intervention occurred.

Bacteriological and serological findings: Seven stool cultures, the first one on 7-11-39 and the last one on 8-9-39, were positive for *Salmonella*, Paratyphoid C group. Similar organisms were recovered from bile obtained by duodenal drainage on 8-3 and 8-4. The bacteria were identified as *Salmonella morbiifcans bovis*. Blood cultures on 7-13 and 7-26 remained

sterile. Serum agglutinins for *S. morbiifcans bovis*: 7-9 and 7-13—negative; 7-19 and 7-20—positive 1:800; on 7-30—positive 1:100. A qualitative examination of the serum of 7-20 revealed agglutinins for the O-antigen and the specific and the non-specific H-antigen of *S. morbiifcans bovis*.

*S. morbiifcans bovis* was first isolated by Basenau (1), 1893, from the organs of a cow which had been suffering from puerperal metritis. Similar organisms were found in another animal, the meat of which had caused an extended outbreak of gastro-enteritis. Since 1926 when Bruce White (2) studied the antigenic composition, this type has been found in England and other European countries as a cause of outbreaks of food poisoning, both sporadic and epidemic in character. The symptoms were described as of the ordinary gastro-enteritis type but cases with a more typhoid-like course are also reported. Some outbreaks were traced back to beef; two outbreaks, recently observed in Germany, to chopped horse meat (3 to 6).

### COMMENT AND SUMMARY

In both our cases, it appears from the course of the disease that the occurrence of *Salmonella* is not coincidental but is actually the etiological factor. This is confirmed by the presence of fully specific agglutinins and by the increase and decrease of the agglutinin titers corresponding to the clinical course of the infections.

The etiological agent found in the first case (*S. typhi murium*) is of the ordinary type of *Salmonella* frequently found in cases of so-called food poisoning. The type of *Salmonella* isolated in the second case, on the other hand, is herewith reported for the first time in the Western hemisphere. Neither human nor animal infections have been mentioned heretofore as far as we know. The source of the infection has not been found in our case. It may be significant, however, that the patient's husband is a butcher. In spite of the fact that this type has not yet been found in animals in this country, an animal origin of the infection is likely in the light of the observations reported from Europe, and it is to be expected that further studies will reveal the occurrence of *S. morbiifcans bovis* also in animals in this country.

It is advisable for the clinician and especially for the surgeon to pay attention to *Salmonella* infections not only in cases of gastro-enteritis and of a typhoid-like type, but also in such patients as described above. The patient upon whom we operated suffered no ill consequences. In other cases, however, the operation may endanger the patient in the same way as an unnecessary laparotomy performed during the course of typhoid fever. It is worth while referring to similar observations made during a recent outbreak of paratyphoid fever in Massachusetts. R. F. Feemster and G. W. Anderson (7) mention four patients who were operated upon for appendicitis before the outbreaks were discovered.

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# Amebic Granuloma of the Rectum and Balantidiasis in the Same Patient

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LITTLE ROCK, ARKANSAS

THE rarity of a double protozoan infection in the same patient justifies my bringing to your attention a case in which amebic granuloma was complicated by a balantidium coli infection. Balantidiasis occurs very rarely, and very few proctologists have had the opportunity of studying it. Nisbet (1) reviewed the American Literature in 1920 and found the following cases reported: Three from Louisiana, four from Arkansas, three from North Carolina, and one each from Iowa, Minnesota, Mississippi, Oklahoma, Maryland and Massachusetts. Logan (2) reported four cases from Minnesota in 1921. McEwen (3) described a case from Kansas in 1924 in which the symptoms extended over twenty-six years. In 1925, Ford (4) found one case in the state of Washington, and Mendelson (5) discovered one case in New Mexico in 1932. Five cases of balantidial dysentery were reported by Scott (6) in 1935 from West Virginia. Young (7) added to this number seven cases from the South Carolina State Hospital in 1939. Meleney (8), in a personal communication to Young, reported two cases in Tennessee. Buie (9) states that he has seen only three patients with balantidiasis at the Mayo Clinic.

Tumor formations, caused by the endameba histolytica, have been described in the literature so rarely that the occurrence of balantidiasis and amebic granuloma in the same patient appears to be so unique as to be worth while reporting. Gunn and Howard (10) reviewed the literature thoroughly in 1931 and described their three cases in detail from the Stanford University Hospital. They stressed the fact that a localized tumor presenting the clinical and gross pathological picture of carcinoma of the large bowel can be caused by amebae. In their cases the clinical symptoms were those of a malignant growth. Runyan and Herrick (11) reported four cases showing massive ulceration and fibrosis, caused by the invasion of the endameba histolytica. They mistook one of their four cases for a tumor of the kidney and another for carcinoma of the cecum. They diagnosed correctly their remaining two cases on the basis of their previous experience on finding amebae in the stool. In 1936 Yeomans (12) reported a case of large granuloma which proved to be caused by the endameba histolytica. Harrison (13), Cope (14), Rogers (15), and James and Deeke (16), mention several cases of granulomatous tumors in the cecum and transverse colon in which a clinical and roentgen diagnosis of a malignant growth was made and which later proved to be amebic infections and resulted in complete recovery with disappearance of the tumor following antiamebic treatment. Not infrequently the thickened bowel was palpable through the abdominal wall. The tumors, encountered by these

authors, were found most frequently in the cecum and the flexures of the colon.

The importance of a differential diagnosis of chronic amebiasis and carcinoma of the large bowel, therefore, must be kept in mind, because chronicity of such symptoms as diarrhea or (rarely) dysentery, mucus in the stool, abdominal pain, chronic invalidism, loss of weight, partial obstruction and tumor formation may be observed in either disease. Amebiasis and carcinoma of the large bowel may be present at the same time.

## REPORT OF CASE

C. W., a World War veteran, aged 49, was referred by Dr. Chas. Reed, Jr., for sigmoidoscopy on November 21, 1938. He complained of chronic diarrhea, occasional attacks of "dysentery," frequent passages of mucus, his stools amounting to ten to twenty in twenty-four hours. He had lost forty pounds of weight and had become a chronic invalid. His family and past histories were irrelevant and his habits were good. While going into Germany with the American army of occupation in 1918, he contracted dysentery. His stools had never been examined nor had he ever been sigmoidoscoped prior to our examination. He complained of marked anorexia, bloating after meals and dull pain in the left lower abdominal quadrant. He had noticed a feeling of incomplete emptying of the bowel after defecation for the past five months. He had taken paregoric or bismuth for the past twenty years to obtain relief from his dysentery and symptoms. He had an appendectomy in 1920, and was operated for hemorrhoids in 1921 and in 1936.

The patient was moderately emaciated and appeared ill and depressed because of leading—what he termed—a "toilet life," which made it impossible for him to pursue an occupation. There was marked tenderness over the descending colon. The urine was negative, and the temperature was 99.8° F. The blood showed a moderately severe normocytic anemia. Hemoglobin (Sahli) was 77 per cent. Red cells were 3,408,000 and white cells 9400 per cmm. A corona of medium sized externo-internal hemorrhoids was surrounding the anus. The sigmoidoscope was passed ten inches without much difficulty and seven inches from the anus, on the right lateral wall of the rectal ampulla a soft, grayish-pink granulomatous growth the size of a large walnut was seen. The edges of the tumor appeared nodular and in the center of the mass were three irregular craters containing necrotic debris. In addition, there were a number of discrete punched out ulcers scattered over the walls of the rectal ampulla and sigmoid. These ulcers were irregular in outline, averaging about  $\frac{3}{4}$  to 1 cm. in diameter, and they bled easily when scraped with the spoon. The mucosa between the ulcers was of normal color, while the base and the circumference of the growth showed hyperemia and thickening of the mucosa.

I was immediately impressed with the idea that these ulcers were caused by an amebic infection and that the tumor was an ulcerating carcinoma of the rectum. Scrapings from these ulcers were immediately examined under the microscope, and, to my surprise, large ovoid motile

parasites were seen, their periphery being uniformly covered with rapidly moving cilia, causing the parasites to move forward with a rotary motion. At the anterior pole of each parasite the funnel shaped cytostome was plainly visible and on the posterior pole the cytophyge or anal opening could be discerned. Two contractile vacuoles were present and the parasites were identified as balantidia coli. No cysts were found.

Scrapings were then taken from the craters and the edges of the tumor in the ampulla and examined microscopically. Many motile trophozoites of the endameba histolytica were seen. A diagnosis of balantidiasis coli and amebic granuloma was made. Treatment was instituted and the patient was given ten tablets of Diodoquin (0.21 gm.) daily for ten days with instructions to return for sigmoidoscopic and microscopic examination. For his anorexia he was given 500 units of Vitamin B<sub>1</sub> and a high caloric, low residue diet. No emetine injections were administered, as I wished to observe the therapeutic effect of this new diiodohydroxyquinoline compound on the balantidium coli as well as on the amebic granuloma.

The patient returned after ten days, having gained ten pounds. He now had only two evacuations daily which he described as solid for the first time in twenty years. His abdominal pain had disappeared, and he enjoyed three meals a day. Sigmoidoscopy showed an amazingly normal looking rectum and sigmoid, no ulcers being visible and the granuloma having melted away following anti-amebic treatment. Only a large irregular scar—4 cm. in diameter—showed at the site of the former tumor.

#### COMMENT AND CONCLUSIONS

The ulcers caused by balantidium coli are clinically indistinguishable from those caused by endameba his-

tolytica. Both protozoa show a marked similarity in regards to clinical symptoms and proctoscopic appearance. Since—as Young (7) pointed out in his recent paper on balantidiasis—a long list of medicaments has been tried and recommended for this infection, and since there exists a similarity in pathogenicity of balantidial to amebic dysentery, both being protozoa, it was decided to try diodoquin, a new hydroxyquinoline compound\* exclusively, to study its effect on this double infection. Stool and proctoscopic examinations gave negative results for five months. The patient felt well and gained twenty-eight pounds during this time.

Diodoquin which was used by the author on forty-one consecutive cases of amebiasis with excellent results seemed to exert an equally good therapeutic effect on amebic granuloma to the complete disappearance of the tumor. It is interesting to speculate as to whether the high iodine content of diodoquin (64 per cent) caused the rapid resolution of the granuloma.

Amebic granulomata may be easily mistaken for malignant growths, for they give symptoms, signs and proctoscopic appearances very similar to those produced by carcinoma.

Amebic granuloma is localized most frequently in the cecum and flexures of the colon—as pointed out by Howard and Gunn and others—but occurs, as in the case reported, also in the rectum. It is slow in developing and occurs in untreated or inadequately treated cases.

\*Manufactured by G. D. Searle & Co.

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## A Technique for Radiographic Identification of a Lesion Seen in the Recto-Sigmoid with the Help of the Sigmoidoscope\*

By

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and

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**O**CCASIONALLY the gastro-enterologist is confronted with the question: Is the lesion seen in the sigmoid loop with the help of the sigmoidoscope the same as that seen in the roentgenogram? The surgeon might like to know before he opens the abdomen if he has to look for one lesion or two.

In the particular case which brought the problem acutely to our minds, sigmoidoscopic examination revealed an edematous, reddened sessile polyp about 20 cm. from the anal orifice. Examination of several biopsy specimens failed to reveal malignant changes. Under fluoroscopic examination the barium enema was seen to be delayed somewhat at a point in the sigmoid loop, and in the roentgenograms an irregularity of outline was noted at that point. The polyp which had

\*From the Radiologic Service of M. G. Wasch, M.D. and the Department of Gastro-Enterology, Division of Medicine, The Jewish Hospital of Brooklyn, Brooklyn, New York.  
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been seen through the sigmoidoscope was not visualized. In order to see if the polyp could be made out with the roentgen ray, the sigmoidoscope was again passed and the lesion was painted with lipiodol. Then on making roentgenograms the polyp was easily identified as it protruded into the lumen of the gas-filled bowel.

Because the suspicious area in the sigmoid was distant from this lesion, the presence of two lesions was strongly suspected. At operation performed by Dr. Louis Berger a carcinoma encircling the bowel was found in the middle of the sigmoid loop. This lesion was resected and proved to be a colloid adenocarcinoma.

## Treatment

According to J. P. Brady, writing in the United States Naval Medical Bulletin for January, 1939, transfusions of blood from patients who have recovered from venereal lymphogranuloma have a curative influence on patients suffering with the disease.

It may be remembered that some physicians have recently claimed good results with sulphanilimide, while others have advised the use of roentgenotherapy.

According to Foshay and Hagebusch, writing in the Journal of the A. M. A. for June 10, 1939, the giving of histamine, either by mouth or intramuscularly, brought marked relief to twenty out of twenty-two patients with serum sickness, most of them with a severe form of this disorder.

In the Journal of the American Medical Association for February 26, 1938, Rynearson reported that the sensitivity to protamine zinc insulin may disappear after injections of histamine or the giving of histaminease by mouth.

According to K. Grunert, writing in the Münchener medizinische Wochenschrift for September 2, 1938, migraine in children is particularly likely to be made worse by difficulties in refraction and accommodation in the eyes.

According to Rusk et al, in the Journal of the A. M. A. for June 10, 1939, patients with acute and chronic urticaria showed an increase in serum potassium. This increase disappeared as the patient recovered. Under such circumstances it might be interesting to try the effect on such patients of corticosterone.

In an editorial in the Journal of the A. M. A. for January 28, 1939, page 332, comment was made on an interesting article by J. A. Glover of England, who has studied the frequency with which tonsillectomy is performed on English school children.

Glover believes that the undoubted brilliant results of tonsillectomy in individual cases have led to the performance of the operation in many doubtful cases. As the Schools Epidemic Committee said, "it is a little difficult to believe that among the mass of tonsillectomies performed today all subjects for operation are selected with true discrimination, and one cannot avoid the conclusion that there is a tendency for the operation to be performed as a routine prophylactic ritual for no particular reason and with no particular result."

Among the greatest needs in medicine today is for more cerebration and more thought in regard to the use of different types of treatment. There is too great

a tendency to use a certain form of treatment in all cases simply because it works well in a few.

Steinbrocker, McEachern, La Motta, and Brooks tried cobra venom in cases of arthritic pain and found slight or moderate relief in one out of five. They were not enthusiastic about the results.

According to Allen Rogers of Morristown, Pennsylvania, a single dose of 100 mg. of nicotinic acid stopped a severe attack of migraine. (Journal of the A. M. A., January 1940, volume 114, page 347). This might be worth trying again.

Curiously, already a report has come in to indicate that the present enthusiasm for the use of potassium chloride in allergic disorders may not be long lived. In a recent number of the Journal of the A. M. A., Dr. David Engelsher wrote that he had tried the method out in sixty-four cases. The patients were given ten 5 grain tablets to be taken when necessary three times a day after meals. It is not clear just what the dose was, but we presume 1 tablet was given three times a day. This would be a smaller dose than that used by some men. At any rate, more than half of the patients not only were not helped but they developed severe epigastric pain and sometimes dizziness, tachycardia and other unpleasant disturbances. Practically the only ones who were slightly helped were those who were given in addition, acetylsalicylic acid.

In the Journal of the A. M. A., volume 112, page 2395, Rusk, Weichselbaum, and Somogyi found that patients suffering with asthma and urticaria had somewhat heightened serum potassium values, between 23.4 and 24.4 mg. per 100 cc. of serum. The giving of an increased amount of potassium in the diet was thought to replace depleted stores of potassium in the tissues. The giving of potassium chloride helped some of the patients, while others were not helped.

According to *Science* for May 19, 1939, Drs. J. Bronfenbrenner, D. M. Hetler, Frances Love and J. M. Burnett of St. Louis, reported at a recent meeting of the American Society for the Study of Allergy that pigs made sensitive to egg white could eat this food if first given enough Vitamin C. When the Vitamin C was removed from the diet and the egg white was given, practically 100 per cent of the animals developed allergic symptoms.

In the Journal of the American Medical Association for August 19, 1939, Dr. J. W. Graham of Toronto, reported that some of the patients who for a few days

are made utterly miserable by intensive roentgen ray treatment can be helped by the giving of nicotinic acid.

In *Science* for April 7, 1939, Holmes, Amberg and Campbell report that lead, when taken into the body, tends to combine with the Vitamin C of the tissues to form a poorly ionized compound which is much less toxic than the original lead. They found that a few painters who for years had eaten a diet unusually rich in Vitamin C had much less lead in the urine than other painters did. Holmes et al, feel, therefore, that Vitamin C in 50 mg. doses might well be used as a treatment for lead poisoning.

B. Bloom and S. Grauman in "Southwestern Medicine" for July, 1939, report good results in many cases of hay fever with good sized doses of potassium chloride. They have given up to 10 grains five times a day. The drug helped also in some cases of chronic sinusitis thought to be of allergic origin. Usually it was of no use in cases of asthma. Fortunately it was of great help in a number of cases of acute urticaria and in some cases of chronic urticaria. Some patients with eczema were helped.

A man who for years suffered with morning diarrhea, which got him out of bed, had to take some mandelic acid for a slight urinary infection. Curiously, this promptly stopped the morning diarrhea. More curious yet, it did not return after the man stopped the use of the mandelic acid.

A note in *Science* for October 13, 1939, states that Dr. Frank J. Novak has pointed out that the danger of producing serious lung lesions in children by the dropping of mineral oil into the nose can be avoided to a large extent if a vegetable oil is used. Apparently the lung can get rid of vegetable oils, but it can't get rid of mineral oil.

In the *Revue Neurologique*, Paris, for July, 1938, Villey and Buvars report hopeful results in the treatment of migraine with intravenous injections of hypertonic solutions of sodium chloride. They used 20 cc. of a concentration of either 10 or 20 per cent.

In the *Archives des Maladies de l'Appareil digestif et des Maladies de la Nutrition* for November, 1938, Kouchelevsky and Milutine claimed that treatment with roentgen radiation over the abdomen will cure a considerable percentage of patients with constipation. Apparently the effect was first noted accidentally.

In the June, 1939, number of the *Annals of Internal Medicine*, Otto Steinbrocker reports having injected watery or oily solutions of procaine into the tissues about painful arthritic joints or around the source of nerve supply to a painful region. He did this to 134 patients with chronic intractable discomfort. Sixty per cent obtained lasting relief of the pain and another 13 per cent were helped. Twenty-one per cent were not helped. The method has been tried by many men, and it would seem as if it should be used even more often in the future.

Stanley Cobb in his review of neuropsychiatry for December, 1939, in the *Archives of Internal Medicine*,

states that enthusiasm is being lost for the shock treatment of the psychoses. Experts are beginning to conclude that satisfactory remissions do not occur so often as was at first represented, and it looks now as if they were no more frequent with the new treatment than they are in institutions where the patients are treated conservatively and given good care. Furthermore, the so-called cures are generally not permanent.

Meniere's disease is said to be relieved often by the administration of potassium chloride in 25 per cent solution, about 6 grams a day.

G. E. Finkle recently stated in the *Journal of the Kansas Medical Society*, volume 40, page 372, that in four cases of paroxysmal tachycardia seen by him the giving of from 1/24 to 1/30 of a grain of apomorphine brought the attack to a close.

In the October 21, 1939, number of the *Journal of the A. M. A.*, there is an article by W. P. Havens describing the case of a woman of fifty-nine who at necropsy was found to have a large mass of colloidal aluminum hydroxide somewhat obstructing the mid-portion of the ileum and also the cecum and transverse colon. It is possible that the formation of the masses in this case was due to the fact that the woman was taking at the same time hydrocarbon oil. The impression left by this report is that care should be taken to keep the bowels moving in the case of patients being given large amounts of the new aluminum preparations.

In the *Proceedings of the Society for Experimental Biology and Medicine* for October, 1939, Engle and Crafts report on the oral use of stilboestrol, a new crystalline synthetic estrogenic substance. Interestingly, the drug seemed to work about as well by mouth as when given hypodermically. Another most encouraging finding was that it seemed to work as well in small doses as in large. No toxic or other untoward effects were observed by Engle and Crafts but other writers speak of nausea and vomiting in about a fourth of the cases. Some men are using this drug in the form of a sterile pellet, which is inserted under the skin of the back.

According to H. A. Hanelin, who writes in the *Michigan State Medical Society Journal* for November, 1939, paroxysmal hiccup of long duration can easily be relieved by inhalations of amphetamine sulfate or benzedrine.

In the *Journal of the A. M. A.* for April 1, 1939, there appeared a note from Dr. Zwillinger of Czechoslovakia, stating that magnesium sulphate is often useful in the treatment of paroxysmal tachycardia. It is to be hoped that this treatment will help many of these much troubled patients.

In the *London Lancet* of September 23, 1939, D. Williams comments on the use of dilantin in epilepsy. He found toxic symptoms in 36 per cent of the patients. The drug was of value in the treatment of some cases when other forms of treatment had failed, but he doubts if one should use it before other less



toxic ones have been tried out. The number of fits were reduced in 79 per cent of the patients with grand mal and in 63 per cent with petit mal.

R. N. Rutherford, in the September 14 number of the New England Journal of Medicine, reported good results in the treatment of severe pain with cobra venom. He generally used either 2 or 3 cc. a day for from four to six days, or until relief was obtained, and then lowered the dose to a maintenance level. Fifty per cent of the patients were completely re-

lieved, and in another 38 per cent there was partial relief.

If there is to be a response to the treatment it usually comes on the third or fourth day and is complete by the sixth or seventh day. If relief is only partial it is not likely to increase after that time. Once relieved, most of the patients were able to keep comfortable with one ampule every other day. Some, however, required two or three a day. The material must be injected into the muscles, as otherwise it causes much local reaction.

## Editorials

### NOTICE

**T**HE A. G. A. meeting will be held in Atlantic City on Monday and Tuesday, June 10th and 11th; the A. M. A. meeting, the same week in New York.

What with large assemblies of physicians attending the A. M. A. meeting, the World's Fair, and the general attractions of the great metropolis, rooms and accommodations will probably be at a premium.

The N. Y. County Medical Society, acting as host to the National meeting, is anxious to be of help from the scientific aspect, and is anxious to afford a cordial welcome to the visiting physicians and their families.

The local sub-committee for gastro-enterology includes Dr. Burrill B. Crohn, Dr. Anthony Bassler and Dr. Frank Yeomans. The section on gastro-enterology and proctology will hold their meetings at the Hotel Roosevelt. It is planned to make special arrangements for visiting the World's Fair; reduced or group rates are being planned and transportation facilities, hotel accommodations, or information in general will be gladly supplied by the members of the sub-committee.

The secretary of the Section on Gastro-Enterology and Proctology of the A. M. A. is of course in the best position to handle all requests for facilities and information, but in addition, the local sub-committee is anxious to place itself at the disposal of members of the national organizations and those interested in the meeting.

As representatives of the N. Y. County Medical Society, they extend a hearty welcome and expectations of an unusually brilliant scientific meeting and social entertainment.

Burrill B. Crohn, New York, N. Y.

**A** MEETING of the National Conference on the Nomenclature of Disease was called and held in Chicago on March 1. The meeting was attended by representatives of many of the important national medical and surgical associations, as well as by members representing the U. S. Veteran's Administration, U. S. Navy, U. S. Army, Public Health Assn., and analogous important groups.

This conference was originally organized in 1932 for the standardization of nomenclature of disease, and published a volume of terms which is being extensively used in all of the larger institutes and hospitals of this country. This handbook has been popular and has been reprinted several times.

Five years have elapsed since the last issue. The present conference in Chicago was called with the idea

of revising and improving and re-editing the present publication.

The section on gastro-enterology constitutes the largest individual section in the book, over 15% of the total list. It was realized that the section was very large and that probably some duplications had occurred, unnecessary terms have crept into the list, and improvements could be made. A new and revised issue is contemplated by the National Conference under the auspices of the A. M. A., and the guidance of Dr. Edwin P. Jordan, the assistant secretary of the A. M. A., whose very helpful cooperation has been of untold advantage.

Criticisms, additions, or deletions of terminology in the list of terms relating to the alimentary tract, would be appreciated and would undoubtedly be very helpful in such a revision. The main idea would be to condense the number of items, eliminating confusion and simplifying the terminology.

The writer was the original chairman of a committee of the American Gastro-Enterological Association appointed to represent this specialty, at the first conference. I am still serving in this capacity and will welcome suggestions and criticisms from anyone who has used the index in hospitals or in the record rooms of institutions.

Burrill B. Crohn, New York, N. Y.

To the Editor:

**I**N the American Journal of Digestive Diseases and Nutrition, 2:14, 1935, I published an article on "The Weltmann Serum Coagulation Reaction in Diseases of the Liver." Since subsequent work on liver disease proved the test of no clinical value, I discontinued studying the reaction. The subject was revived in 1937 by Levinson (J. of Lab. and Clin. Med., 23:53, Oct., 1937) and again in 1939 (Annals of Int. Med., 12:148, June, 1939). These articles led me to re-investigate the reaction. I have performed Weltmann's test on the sera of more than five hundred consecutive patients with gastro-intestinal complaints.

I wish to present one significant finding. There were eight cases of penetrating ulcer. Uniformly in these cases there was a shift to the left with readings of from four to two. This is apparently more reliable evidence of penetrating ulcer than is the sedimentation rate. In two cases of posterior wall ulcers near the esophagus, missed on X-rays but found at operation, the coagulation band was diminished. In the presence

of gastric symptoms with a shift to the left of the coagulation band every effort should be made to roentgenologically or gastroscopically demonstrate a posterior wall penetrating ulcer.

It is hoped that investigators who have at their disposal a large number of ulcer patients will further aid in determining the value of this reaction.

Manfred Kraemer, Newark, N. J.

### THE GASTRIC ELIMINATION OF NEUTRAL RED AS A HELP IN THE DIAGNOSIS OF SPRUE

By A. Rodriguez Olleros, M.D., from the University Clinic of Therapeutics at Madrid, Spain, and F. Hernandez Morales, M.D., from the Department of Clinical Medicine, School of Tropical Medicine, San Juan, P. R.

AS is well known, sprue resembles pernicious anemia so closely that occasionally there is difficulty in making the differential diagnosis. Rhoads and Miller (1) said that "the only difference between certain cases of sprue and pernicious anemia was that a substance rich in the water soluble vitamin was therapeutically effective *per se*, at least, in certain cases of sprue, whereas, it was effective in pernicious anemia only after it had been incubated with normal gastric juice." In a former publication (2) we reported the gastroscopic findings in 28 cases of tropical sprue. We noted the presence of atrophic gastritis in one form or another, sometimes generalized, sometimes localized. The lesions were in general less marked than those observed by various authors in pernicious anemia (3, 4, 5). As in pernicious anemia, so in sprue, liver therapy improved the gastroscopic aspect of the mucosa. A recent report by Schindler and Serby (3) of the gastroscopic findings in 23 cases of pernicious anemia corroborates the conclusions and strengthens the opinions expressed by other authors that from the gastroscopic study alone, it is not possible to differentiate doubtful cases of sprue and pernicious anemia.

Under these circumstances any test which would help in the differential diagnosis of sprue and pernicious anemia should be welcomed.

While studying the elimination of neutral red by the gastric mucosa of patients with tropical sprue, we observed that in spite of the existing atrophy of the mucosa of the stomach the dye was eliminated. In pernicious anemia, on the other hand, the elimination of neutral red by the gastric mucosa does not take place. If these observations should be verified by other workers, a helpful test will be available for the differential diagnosis of the two diseases.

### MATERIAL AND METHOD

We studied 29 patients in the clinic of the University Hospital of the School of Tropical Medicine. With the exception of one, who suffered from pellagra, all had been diagnosed by the Department of Clinical Medicine as having sprue. In all of them we performed the neutral red test in connection with a fractional examination of the gastric juice (1). The method, with slight modification, is that used by Katsch and Kalk (6). After a 12-hour fast, a solution of 0.2 gm. of caffeine in 300 cc. of water with two drops of a solution of methylene blue was used as the stimulus to secretion. After the stomach had been emptied of this, 5 cc. of 1 per cent neutral red was in-

jected intramuscularly. When free hydrochloric acid was not obtained with caffeine, we gave histamine. After the injection of neutral red the gastric contents were aspirated every five minutes until a pink color appeared.

### RESULTS

In the 29 cases studied the curve of gastric acidity was hyperacid in 4 (13.8 per cent); normal in 6 (20.7 per cent); hypo-acid in 11 (37.9 per cent); anacid in 8 (27.6 per cent). Of the anacid, 3 were refractory to histamine.

In the hyperacid group, the average latent period before elimination of the neutral red was twelve and a half minutes, in the normal, eleven and six-tenths minutes, in the hypo-acid, seventeen and seven-tenths minutes, and in the anacid, twenty-two and a half minutes. The average latent period was sixteen minutes.

On comparing these values with those found in patients from various countries and with different maladies, but with the same types of gastric acidities as in our sprue cases, we noticed that the elimination of the neutral red by the gastric mucosa in cases of sprue is more rapid.

Piersol, Bockus and Bank (7) noted in hyperacid patients without sprue an average latent period for elimination of neutral red of twenty-three minutes; with normal acidity it was fourteen and a half minutes, and with hypo-acidity it was thirty-two minutes. Katsch (8) in Germany in cases with hyper-acidity found times of from four to ten minutes; with normal acidity they were from fifteen to twenty minutes, with hypoacidity or anacidity they were from thirty to ninety minutes. Held (9) in France found in the hyperacid, four to fourteen minutes; with normal acidity, seventeen minutes; with hypo-acidity, twenty-six to forty minutes, and with anacidity (with caffeine) forty-five to ninety-five minutes.

Rodríguez-Olleros and Viesca (11), working with tuberculous patients who showed approximately the same distribution of gastric acidities as was found in our patients with sprue, found an average elimination time of thirty-five minutes.

Among the cases studied we have included a case of pellagra and one of sprue with a histamine resistant achlorhydria, in both of which the neutral red was not eliminated. We are inclined to believe that the case diagnosed as sprue is really one of pernicious anemia, for upon reviewing the clinical history we find a record of neurological changes.

In 21 of our 28 patients gastroscopy was done. In most of them there were lesions of a predominantly atrophic type of gastritis. This is important, because Held (8), and Henning and Jurgens (11) hold that this type of gastritis not only modifies the hydrochloric acid secretion but retards the elimination of neutral red.

### COMMENTS

Ashford (12) found anacidity in 38 per cent of his cases of sprue. Suárez (13) found hypochlorhydria or achlorhydria (histamine resistant) in almost every one of 150 cases studied. Rodríguez-Molina (14) found achylia in 32 per cent of his patients.

Curiously, then, in spite of the atrophy of the gastric mucosa which should retard the elimination of neutral red, in sprue the dye is excreted more quickly than in other patients with a low acidity.

In pernicious anemia, the gastric mucosa is so atrophic that it does not secrete hydrochloric acid and it does not eliminate neutral red (4, 5).

Apparently in sprue the gastric mucosa does not atrophy so completely as it does in pernicious anemia.

### CONCLUSIONS

Patients with sprue begin to eliminate neutral red through the gastric mucosa sooner than do patients with other diseases and the same degree of gastric acidity and a similar atrophic gastritis. Since patients with primary anemia do not excrete the dye, the use of neutral red can be used as a help in differential diagnosis in puzzling cases.

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### CHRONIC VITAMIN B<sub>1</sub> DEFICIENCY IN THE ETIOLOGY OF MEGAESOPHAGUS AND MEGACOLON

SINCE 1932 the subjects of megaesophagus and megacolon have received much attention in Brazil, where the disease appears to be unusually common. This can be seen from the fact that Etzel was able last September to analyze a series of 626 cases seen between the years 1920 and 1938. Of these patients, 569 were born in Brazil and 57 were born abroad. In 1937 Edmundo Vasconcelos and Gabriel Botelho had enough material to publish a 434 page book on megaesophagus alone.

The old theory of a congenital defect in the local nerve plexuses or in the extrinsic nerves of the esophagus which was brought forward by Hurst, Rake and Cameron has not been accepted by the Brazilian workers. To be sure, they have found marked destruction of Auerbach's plexus in cases of cardiospasm and megacolon, but now the Brazilian pathologist, Eduardo Etzel believes that this injury is brought about by a deficiency in the Vitamin B<sub>1</sub> content of the diet. In careful studies he has described the several stages of the injury done to the plexus.

It is interesting to note the association between megaesophagus and megacolon and also the geographic distribution of patients with the disease. (See Etzel, O., Hospital, 16:445-455, September, 1939). These associated diseases seem to attack people in the rural districts where the food is not so good as it is in cities on the Brazilian coast. There the inhabitants have plenty of fish and a greater variety of food. The sufferers come largely from regions where salaries are very low and the diet is poor and inadequate. The food there consists largely of carbohydrate, and it contains too little Vitamin B<sub>1</sub>. In some areas megaesophagus appears to be endemic in nature. For twenty-five years Brazilian physicians have been pointing to the

correlation between what is called tropical dysphagia and a deficient diet.

Etzel found that 92 per cent of his 28 Italian patients with megaesophagus and megacolon came from Veneto, a district where pellagra is common and where much "polenta" or cornmeal is consumed.

It will be interesting to see now if megaesophagus and megacolon can be treated successfully with a better diet.

G. S. de Paula e Silva, Bello Horizonte, Brazil.

### THE NORMAL RANGE OF GASTRIC ACIDITY

WHAT is normal gastric acidity after an injection of histamine? In the June, 1939, number of the Annals of Internal Medicine, Julian M. Ruffin and Macdonald Dick reported a statistical study of gastric acidity after histamine stimulation in 2877 patients, 1917 of whom showed no evidence of disease.

The results of the study were similar to those reported several years ago by Vanzant and her co-workers. The main difference was that there was a wider range of variation with histamine than with the Ewald meal. In two-thirds of the cases the free acid values ranged from 30 to 85 units. Actually, this range after histamine stimulation is so great that Ruffin and Dick were unable to say what values should be taken as representing normal acidity, hyperacidity, or hypoad acidity. They came to the conclusion that when histamine stimulation brings out free hydrochloric acid in the gastric juice, the actual level of this acidity is of little, if any, diagnostic significance. These conclusions coincide with those of other investigators.

Years ago Comfort found that, except perhaps in the case of primary anemia, the results of gastric analysis with histamine were no more useful diagnostically than are the results with the Ewald type of meal. Unfortunately the value of gastric analysis with an Ewald meal is small. Some results are suggestive but none are pathognomonic of anything.

The incidence of achlorhydria in the whole group of persons studied was 11 per cent. It ranged from 0 in youth to about 25 per cent after the age of sixty years.

W. C. A.

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### THE MAKING OF NEUROSES IN ANIMALS AND MAN

EVERY physician today who has to deal often with persons who are broken down nervously will be interested in the studies that are now being made by experimental psychologists on rats and other animals. Particularly interesting is the work of Norman R. F. Maier (Studies of abnormal behavior in the rat,

Harper and Brothers, \$2.00) which was reported at the 1938 meeting of the A. A. A. S. and there awarded the \$1,000 prize for the best paper presented.

Maier trained rats to jump from a little platform through either one of two windows distinguished by cards with different devices. After some forty or fifty tries the rat learned that his food was back of one of the cards and that this would easily swing out of the way when he jumped at it. When he jumped at the other fixed card, he bumped his nose and fell into a net below. After the rat had become accustomed to this situation and sure of where his food was, Dr. Maier began either to switch the cards until the poor harrassed rat realized that he didn't know where to jump, or else he gave the rat only one window to jump at, with the wrong card on it. Under these circumstances the rat soon refused to jump, but then a jet of air was turned on him and he was made so uncomfortable on his little platform that finally he had to jump. Under such circumstances the rats developed a number of curious reactions: some went into convulsions; others assumed catatonic positions with their little fists clenched; others started to hop around in a curious way; others developed tics, and some went into a passive stage in which they "played possum" and appeared to be almost dead.

Curiously, then, rats can become highly neurotic and can develop abnormal forms of behavior when they find themselves in a bad situation from which there is no obvious way of escape. They must act, but this means that they must do something which they know is either useless or hurtful. They are trapped in a situation from which there seems no good way out.

How often one finds human beings going into neurosis under just such circumstances—the woman whose marriage is unbearable, but who cannot get out of it because if she does she and her children will be left penniless or almost so, or the girl who is so

anxious to marry but who cannot because she must go on supporting aged parents. We see also the soldier developing hysterical blindness or paralysis or deafness in the front trenches, where to go backward means death as a deserter, and to go forward means death at the hands of the enemy.

As Maier points out, it is interesting that just as with man, so with rats, in less serious situations one finds them developing not neurosis with highly abnormal behavior, but only nervousness and increased irritability. Cats that are subjected to psychologic strain and forced to make unpleasant choices may begin to cry; they will urinate frequently, and they will show other signs of extreme nervousness and mental distress.

Interestingly, it has been found possible, by breeding, to get one strain of rats that is highly neurotic and another that is fairly immune to psychic strain. As most persons know, a rat hates sunlight and open spaces, and hence, to make him comfortable laboratory workers fill his cage with waste paper under which he can burrow and hide. Just put rats out into a large tub where they cannot hide themselves and many will become nervous and upset and, like a college student at an examination, will urinate at frequent intervals. The more nervous ones will defecate. By inbreeding on the one hand those that defecated, and, on the other hand, those that showed little sign of nervousness, it has been possible to produce two strains of rats: one highly nervous and the other fairly stolid.

Much of this sort of thing can be done in the case of man in one generation when a tense, nervous, hypochondriac of a university professor marries a frail, fussy old maid school teacher with a bad case of sore colon. The only child of such a union will often keep many doctors busy for some fifty years.

W. C. A.

## Abstracts

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ARNHEIM, ERNEST E. AND NEUHOF, HAROLD.

*The Severe Forms of Acute Appendicitis; with Special Reference to the Treatment of Appendiceal Abscess. S. G. O., 70:1-42, Jan., 1940.*

This study is based on the personal experiences of Drs. Arnheim and Neuhoof between 1931 and 1939 in severe cases of acute appendicitis. They believe that through the use of certain principles of management and improved surgical technique, there is little reason for fatalities. 212 cases of appendicitis were operated with 4 deaths, a mortality rate of 1.8 per cent. In 3 of the patients who died, diffuse peritonitis was present at the time of operation. There were no deaths in cases of acute appendicitis with abscess or with local peritonitis.

Suggestions for pre-operative treatment and how to decide when the time is right for operation are offered as well as the operative procedure and post-operative treatment. Acute appendicitis and appendiceal abscess are dealt with separately.

The operation is usually delayed if diffused peritonitis,

which can be determined by abdominal pressure, is present. The choice of anesthetic depends on the patient though avertin with or without ether is most common. The incision should be large enough to allow full view and isolation of the lesion and the place should be as nearly over the location of the lesion as is possible. This is where the localized tenderness on palpation or the mass is situated. Directions are given on how to remove the appendix with only the use of instruments, and indications for drainage are included.

Intravenous injections of glucose and saline should be given before, during and after the operation in seriously ill patients. Complicating intra-abdominal suppurative foci are looked for to insure early discovery.

Special attention is given to the management measures of appendiceal abscess to insure low mortality. It is advised that operation be deferred until acute manifestations have subsided; (2) during operation, complete exposure and walling off of the abscess by packs; (3) entry of the abscess through a plane of cleavage, which is developed

progressively; (4) complete evacuation of all recesses of the abscess or abscesses; (5) meticulous "no touch" technique of removing the appendix; (6) removal of the appendix usually; (7) drainage of all abscess cavities by gauze packs.

Francis D. Murphy.

ZWINGLI, F.

*Haut- und Schleimhauttyp des Plattenepithelcarcinoms der oberen Luft- und Speisewege; ihre Beziehungen zur Atrahlenempfindlichkeit. Zeitschr. Krebsforsch., 49(1):109-136, 6 figs., 1939.*

In 1349 biopsies made from the upper alimentary and respiratory tracts in the years 1920-1935 at the pathological institute of the University of Zurich, 456 showed squamous cell carcinoma of cutaneous type, 127 of mucous type, and 104 were of mixed character. Of these, 181 were treated at the roentgenological institute. In general, those of mucous type were much the more radiosensitive. But this was subject to local variation, as in the larynx and pharynx, where all of these cancers were unusually susceptible to irradiation. The least susceptibility to irradiation was shown by cutaneous type cancers of the tongue. —H. E. Eggers (Courtesy of Biol. Abst.).

BELLIS, CARROLL J. AND WANGENSTEEN, OWEN H.

*Venous Circulatory Changes in the Abdomen and Lower Extremities Attending Intestinal Distention. Proc. Soc. Exp. Biol. and Med., 41(2):490-498, 1939.*

Following exptl. intestinal distension with air, the venous pressure in the lower extremities of dogs is elevated, closely paralleling the rise in intraperitoneal pressure. There is an associated delay in the return of blood from the lower extremities, as determined by the sodium cyanid method. Following an initial slight rise of arterial and portal pressure, the former falls progressively to shock level with increasing distention; the portal pressure, however, falls to a constant subnormal plane. The mesenteric venous pressure, similarly falls to a constant level. There is no significant change in inferior vena cava pressure. The shock so produced is explained by the impediment to the return of blood from the lower extremities and by the transperitoneal exudation of blood, and can be relieved by transfusion, decompression, and the steep Trendelenburg position. Clinical cases of intestinal obstruction show an increase of venous pressure in and a delay in the return of blood from the lower extremities proportional to the degree of distention. — (Courtesy of Biol. Abst.).

ROE, JOSEPH H. AND DYER, HELEN M.

*Relation of Nutrition to Gastric Function. I. An Experimental Method. Proc. Soc. Exp. Biol. and Med., 41(2):603-606, 1939.*

An exptl. procedure for studying the relation of nutrition to gastric function, using the rat as the subject, was developed. The data for total acidity, free HCl, and mucin of the gastric juice of the rat following stimulation by acetylcholine chloride and by histamine were found comparable to the values for these constituents in the gastric juice of man. — Authors (Courtesy of Biol. Abst.).

AUER, JOHN AND SEAGER, LLOYD D.

*Simultaneous Observations of Pancreatic and Biliary Papillae of Rabbit. Proc. Soc. Exp. Biol. and Med., 41(2):481-482, 1939.*

The activity of the widely separated biliary and pancreatic papillae of rabbits, narcotized by sodium barbital, was studied by 2 observers at the same time. The following drugs given intraven. had a greater effect on the pancreatic than upon the biliary papilla: Crude secretin 0.5

cc. per kg.; purified secretin (S I of Ivy) 0.1 to 2 mg. per kg.; cholecystokinin (Ivy) 8 mg. per kg. acetylcholine chloride 5 to 100 per kg.; and arecoline hydrobromide 5 to 20 per kg. The biliary papilla was affected more than the pancreatic by histamine hydrochloride 10 to 200 per kg. The frequency and strength of contractions in both papillae was increased by physostigmin sulphate 150 per kg. The activity of both papillae was temporarily abolished by epinephrine hydrochloride 50 to 100 per kg. and by atropine sulphate 50 per kg. —J. Auer (Courtesy of Biol. Abst.).

WANGENSTEEN, OWEN H.

*Aseptic Gastric Resection: I. A Method of Aseptic Anastomosis Adaptable to Any Segment of the Alimentary Canal (Esophagus, Stomach, Small or Large Intestine); II. Including Preliminary Description of Subtotal Excision of the Acid Secreting Area for Ulcer. S. G. O., 70:1-59, Jan., 1940.*

The author states that up until the present time most surgeons used the open method of intestinal anastomosis and until one year ago he too was of this school. For the past year he has used a closed aseptic method of anastomosis with such gratifying results that he was forced to publish it. The closed method is one of his own which he describes fully. This method of anastomosis may be used to make anastomosis anywhere along the alimentary canal; between the lower esophagus and jejunum after total gastrectomy; between the stomach and jejunum after partial gastrectomy; between segments of small and large intestines as well as anastomosis of the small intestine to the colon.

In the operation described, the surfaces to be anastomosed are held in the Payr clamp after the tissue to be excised has been removed by the cautery. Thus, two cauterized ends are brought together. The anastomosis is then completed with a double anterior and a double posterior layer of sutures. After the anastomosis has been completed, the stoma is opened by digital manipulation. For this operation he uses an angle incision along the left costal margin.

The surgeons who have used radical measures of gastrectomy for dealing with ulcers have done so because they felt as Edkins pointed out, that the stimulus for hydrochloric acid secretion came from the antrum. The author felt these procedures did not reduce the acidity and devised an operation where the fundus and the greater curvature was excised and then a gastrojejunostomy done to further reduce the acidity. There are three different methods described, all using the aseptic technique. He has completed seven such operations with good results.

Francis D. Murphy.

OPPENHEIMER, ALBERT.

*Gas in the Bowels; Observations and Experiments in Man. S. G. O., 70:1-105, Jan., 1940.*

This study originated in the observation that on roentgenograms, gas in the bowels is often present when it is not wanted and absent when expected. It covers experiments performed over a period of nine years and includes observations on about 400 men on ways to eliminate gas.

It was found that the intestinal tone determines the amount of gas present in the bowels and the symptoms induced by it. Usually, when gas exceeds a certain amount, it is expelled almost automatically by exciting peristalsis. Consequently, when gas is produced in a large amount, it is not increased in the normal bowels.

Little gas was found in patients complaining of distention. When the intestinal wall is irritable and hyper-tonic, small amounts of gas tend to stimulate peristalsis and eliminate themselves, feeling like distention. Some-

times, when there is no pain or distention, large amounts of gas fill the intestines when the bowels are not acting normal, as when there is renal or biliary colic. The viscera affected was chemically or mechanically stimulated to produce in man, experimentally, acute atony with sudden expansion of gas. Pain and distress accompany gaseous distention when the intestinal muscles resume normal motor function after atony or when they are still contractile.

From experiments, it was noted that the gas obscuring the viscera on roentgenograms of patients having colic was a sign of intestinal atony rather than increased fermentation. When the colic subsides is the best time to try to get rid of gas. Persistent belching and gastrocardiac syndrome are not caused by the amount of air in the stomach. It is thought that gastrocardiac syndrome is a cause rather than a manifestation of cardiac disorder.

Gas in the abdomen without pain is best treated by methods which improve the blood circulation in the abdomen. Flatulence due to fermentation or colonic irritability is controlled by dietary measures, but not by cathartics since they tend to increase irritation.

From the above, it is believed that the old clinical distinction between meteorism, increased colume, and flatulence, increased elimination of gas, should be re-emphasized as the two conditions have little in common.

Francis D. Murphy.

BRUNSCHWIG, ALEXANDER, CLARKE, T. HOWARD, VAN PROHASKA AND SCHMITZ, ROBERT L.

*A Secretory Depressant in the Achlorhydric Gastric Juice of Patients with Carcinoma of the Stomach.*  
S. G. O., 70:1-25, Jan., 1940.

From previous experiments, it was decided that in pernicious anemia, there may be an excess of gastric secretory depressant in the stomach. Gastric juices from patients with and without pernicious anemia were injected into dogs with gastric pouches.

This article tells of the injection of gastric juices from patients with carcinoma of the stomach. From 27 patients with carcinoma of the stomach, samples of achlorhydric gastric juice were taken. They were tested for gastric secretory depressant action by intravenous injection into dogs with stimulated gastric pouches. Twenty-one samples or 78 per cent produced an inhibitory action upon pouch secretions. Similar effects were obtained in 20 per cent of 80 samples of controls from patients not presenting carcinoma of the stomach, or if so, with normal or hyperchlorhydria.

If the juice was boiled for 10 minutes, the depressant factor contained in it was inactivated.

Francis D. Murphy.

LAYNE, JOHN N. AND BERGH, GEORGE S.

*An Experimental Study of Pain in the Human Biliary Tract Induced by Spasm of the Sphincter of Oddi.*  
S. G. O., 70:1-18, Jan., 1940.

This article deals with the disease of the extrahepatic biliary tract which is characterized by a colicky pain that occurs in the epigastrium or right hypochondrium and often radiates to the subscapular or interseapular region. Layne and Bergh made studies of 30 people who had previously undergone choledochostomy and intubation of the bile duct.

Salt fluid was injected under pressure to bring about distention of the common bile duct. This sudden distention induced deep gastric or right upper quadrant pain in all but one of the patients, and the pain radiated to the right subscapular or interseapular area in eleven patients. In some cases, spasm of the sphincter of Oddi was produced by sudden distention and a more intense pain resulted

than from simple distention. If the pressure was removed, the pain stopped within a minute and then the spasm subsided.

Pain in the back followed the pain in the epigastrium or right hypochondrium by about 30 seconds in eleven of the patients. Patients found that the pain in the epigastrium or right upper quadrant was very much similar to the pain of the former biliary tract disease. The muscles of the abdominal wall became very rigid with the pain, but disappeared when the pain or pressure was discontinued. Vomiting, nausea and belching occurred during the experiment in some of the patients.

Francis D. Murphy.

ZOLLINGER, ROBERT.

*A Method of Valvular Cholecystgastrostomy.* S. G. O., 70:1-71, Jan., 1940.

A series of experiments on five dogs was performed to try to produce a valve for cholecystgastrostomy as well as to test the effectiveness of a constructed valve in preventing regurgitation of gastric contents within the biliary tree.

The procedure proved a simple undertaking and can be performed on poor risk patients under local anesthetic. The experiments showed that the gall bladder will remain viable when imbedded for a distance in the wall of the stomach, and a valve was formed which seemed to stop regurgitation of stomach contents into the gall bladder and yet allowed satisfactory drainage of the bile.

A valvular cholecystgastrostomy was performed on four patients with obstruction of the common bile duct from carcinoma. No difficulty resulted from bleeding. In three operations, the fundus was pulled within the lumen of the stomach before the experimental evidence indicated the necessity of anastomosing the fundus of the gall bladder directly to the mucous membranes of the stomach. This may be of advantage in early cases of carcinoma if prolonged survival is quite certain or if there is to be subsequent resection of the neoplasm.

More work must be done to prove or disprove the effectiveness of valvular cholecystgastrostomy in lowering the incidence of ascending biliary infection.

Francis D. Murphy.

## CORRECTION

Due to an oversight, certain corrections made in the proof of the paper by Drs. D. J. Sandweiss and M. H. F. Friedman on "The Use of Urine Extracts in the Treatment of Ulcers," American Journal of Digestive Diseases, January, 1940, page 50, did not appear in the paper. These corrections appeared in the reprint of that article and are as follows:

"Pregnancy urine extract (Antuitrin-S) has no effect on human gastric secretion when administered subcutaneously or intramuscularly in daily doses up to 4 cc. (7, 2). Preliminary observations indicate that the same results are obtained when normal female urine extract is administered intramuscularly in single 5 cc. doses, as determined by the double histamine test described by Rivers (8)."

"Definite diminution in free acid secretion was found in about 50% of a series of ulcer patients to whom urine extract was repeatedly administered for varying periods of time. However, one cannot definitely state that the lower acid secretion is due to the injections of the extract, since similar results have been noted in patients treated by other methods. This study is being continued."

Supervising Editor.

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## PRELIMINARY PROGRAM of

### ANNUAL MEETING

JUNE 10TH AND 11TH

ATLANTIC CITY, N. J.

The meeting will again be held at the Hotel Claridge, which has agreed to a reduction in rates applying not only to the period of the meeting, but for several days before and after. If enough members arrive a couple of days before the meeting, social meet-

ings and trips can be arranged, getting the members better acquainted.

The meeting days are the first two days of the meeting of the American Medical Association in New York City. As on our second day we shall meet only in the morning, our members may leave in the early afternoon and still get to New York in time for all the important events of the meeting there.

The Secretary will appreciate information regarding the decease of any members, so that memorial addresses can be arranged for.

The Official Program will go out to members thirty days before the meeting. The order of the papers will not necessarily be that shown in the following preliminary program:

MONDAY, JUNE 10TH, 9:15 A. M.  
(Daylight Savings Time)

In Memoriam: Dr. William J. Mayo, by George B. Eusterman; Dr. Alexius T. McGlannan, by Julius Friedenwald; Dr. Dudley D. Roberts, by James T. Pilcher.

Factors in the Diagnosis of Intestinal Protozoa in Man and in the Interpretation of the Findings—James L. Borland, Jacksonville.

Esophagitis—Leon Bloch, Chicago.  
The Occurrence of Gastritis as Diagnosed by Gastroscopy in Gastric Neuroses—Julian Meade Ruffin, Durham, N. C.

#### GROUP OF FIVE MINUTE PAPERS AS FOLLOWS:

Gastritis, with Peptic Ulcer Syndrome—Andrew B. Rivers, and (By Invitation) Lucian A. Smith, Rochester.

Spontaneous Variations in Gastric Secretion in Response to Histamine Stimulation—Walter Lincoln Palmer, and (By Invitation) Joseph B. Kirchner and Paul B. Nutter, Chicago.

The Comparative Ph Values Within the Stomach, Pylorus and Duodenum in Antacid Therapy — James B. Eyerly, Chicago.

Correlation of Antral and Bulbar Pressures with Fluoroscopic Observations During Gastric Evacuation—J. P. Quigley, and (By Invitation) J. M. Werle and Daniel Brody, Cleveland.

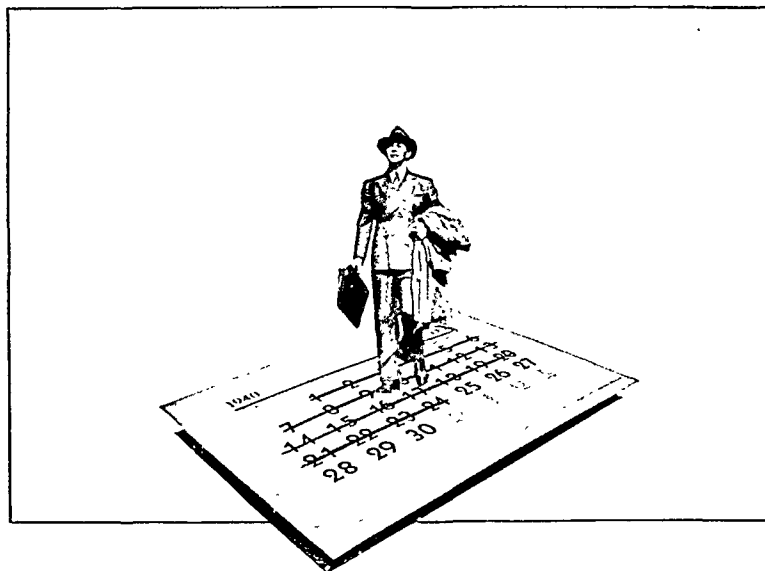
The Secretin Test in the Study of Pancreatic Function—Joseph S. Diamond, Sigmund A. Siegel, Samuel Myerson, New York City. (This presentation is by invitation and will be introduced by Dr. John L. Kantor.

The Presence of Spirochetes in Human Gastric Mucosa—Louis E. Barron, and (By Invitation) A. Stone Freedberg, Boston.

Congenital Diaphragmatic Hernia—John H. Willard, Philadelphia.

MONDAY, JUNE 10TH, 2:15 P. M.

The Effect of the Pituitary Gland on the Digestive Tract. An Experi-



## The LAROSTIDIN treatment of peptic ulcer

*Many patients remain  
ambulatory during  
the entire course  
of 24 daily injections*

Larostidin is a remedy that offers the prospect of prompt relief of symptoms in new peptic ulcer cases as well as those that have run the gamut of diet-and-alkali management, antispasmodics, analgesics, and protein shock. Just how Larostidin acts is not known. But it does bring relief. Commenting on the therapeutic value of Larostidin (histidine) the J.A.M.A. in Current

Comment, November 21, 1936, states: "Combined with more conventional methods of treatment, however, histidine may be regarded as a useful adjunct even though no accurate knowledge exists concerning its mode of action in relieving pain."

In most cases neither a rigidly restricted diet, nor hospitalization, nor home confinement is necessary. Furthermore, results with Larostidin usually follow quickly. The vicious circle of despondency, anorexia, hyperacidity, gastric discomfort, and malnutrition is interrupted, so that it is not unusual to see these patients make appreciable gains in weight and nutrition. Larostidin gets the working man back to his job quicker.



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# Extrarenal Azotemia in Gastro-Intestinal Hemorrhage

## (I) General and Clinical Consideration

By

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**I**N certain renal diseases there is deficient nitrogen excretion with a rise in blood non-protein and urea nitrogen. This state is known as renal azotemia. In recent years an azotemia has been found in a number of disease states for which no renal lesions can be demonstrated. This is spoken of as extrarenal azotemia. Our particular interest in the problem of extrarenal azotemia is in that type which accompanies gastro-intestinal hemorrhage.

We have studied the records of a number of patients admitted to the Scott and White Clinic in order to evaluate the importance of this state in gastro-intestinal hemorrhage. Before studying patients in whom massive hemorrhage occurred, we reviewed 50 case histories of patients with peptic ulcer who were bleeding slightly or not at all. In none of these patients was there significant alteration in the blood urea value (average 26 mg. per cent) or in the erythrocyte count (average 4.62 millions per cmm.). We reviewed also the records of four patients with gastric carcinomas. Gastric carcinomas usually bleed to some extent, but only occasionally do they give rise to a large and fatal hemorrhage. These patients did not show a high blood urea. It appears then that gastric and duodenal ulcers and carcinomas without active hemorrhage do not produce a rise in blood urea. Furthermore, the usual treatment for peptic ulcer does not influence the blood urea value.

We next studied six patients with recent large gastro-intestinal hemorrhage. The following case history is characteristic of the group.

### CASE REPORT

A forty-six year old man had had, some fifteen or twenty years ago, periods of epigastric burning pain relieved by food or alkalis, and usually associated with some melena. He had been free of this trouble until three years prior to the present admission, during which time he had several slight similar attacks but without melena. Ten days prior to admission, he passed a single tarry stool. Nine days before admission, he had epigastric pains, more tarry stools and in the interval these symptoms gradually increased in severity. Three days before admission he vomited a considerable amount of coffee-ground material. At the time of admission to the Clinic, his blood pressure was 116 systolic and 88 diastolic with a pulse rate of 96 beats per minute. There was tenderness in the mid-epigastrium and some slight rigidity in this area. Roentgenologic examination disclosed a markedly dilated stomach. The urinary specific gravity was 1.022 with no evidence of albumin. The leucocyte count was 14,000 on the day of admission, but by the third day dropped to

normal and remained so throughout the balance of his stay in the hospital. The remainder of his laboratory findings are summarized in the accompanying chart.

He was given transfusions as indicated on the eighth, tenth and twenty-second days after admission. It was significant in view of the findings of several authors whose work will be discussed later, that in this patient the urinary chlorides reached a very low level. This was in accord with the plasma chloride findings which are summarized in Chart 1. Relatively

CHART 1—LABORATORY STUDIES ON CASE VI.

Date	BLOOD		CHEMISTRY		URINE	
	Erythrocytes (in millions)	Bl. Urea (mgms. %)	Bl. Chlorides (as NaCl) (mgms. %)	Urine Chlorides (as NaCl) (mgms. %)	Output (in cubic centimeters)	Sodium Chloride (in grams intravenously)
3-21-39	3.61	90.0				
3-23-39		60.0	495.0		1560	14.4
3-24-39	2.29	41.0	419.0	SL-TR.	1920	7.2*
3-25-39					1260	14.4
3-26-39				30.0	1800	7.2
3-27-39	2.10	39.0			1890	7.2
3-28-39						14.4
3-29-39	2.44	39.0				14.4
3-31-39				NONE		14.4
4-2-39						14.4
4-3-39	2.90	33.0				7.2
4-4-39						14.4
4-5-39				693.0		7.2
4-6-39						14.4
4-7-39	3.43			330.0		7.2
4-14-39	Gastro-enterostomy for bleeding duodenal ulcer. Convalescence uneventful.					
5-5-39	Dismissed.					

large doses of sodium chloride were given intravenously as normal salt solution. The urinary output in this patient was maintained between 1200 to 1800 cubic centimeters per day. It is particularly notable that the blood urea returned to approximately normal levels before the plasma chloride or the urinary chloride began to show any significant rise. This would indicate that the blood chloride concentration per se has little to do with the elevation in blood urea.

In an attempt to clarify the cause of this syndrome, we have reviewed the current literature on the subject of azotemia in gastro-intestinal hemorrhage.

In May, 1935, Christiansen stated that in the majority of the 21 cases of fatal gastro-intestinal hemorrhage which he reviewed, the symptoms were more of intoxication than of anemia. He believed that the extreme exhaustion occasionally noted was due to extrarenal azotemia which developed. In this article, he cites in detail two cases in both of whom there was

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a high blood urea value after the gastro-intestinal hemorrhage. In both cases there was no vomiting and in both there was an absence of urinary sodium chloride at the time of the high blood urea determinations. With the administration of sodium chloride there was considerable clinical improvement in both of these patients. The blood urea value approached normal and sodium chloride in the urine increased. With the cessation of sodium chloride administration, urinary sodium chloride dropped and the blood urea values again became elevated.

Borst has given added value to these statements of Christiansen in a review of his own patients. Borst found a hyperchloremia with a low urinary chloride excretion in most of the patients with azotemia due to massive gastro-intestinal hemorrhage. This has been contrary to our experience.

Borst studied three patients and made several important observations, primary of which was that the hyperazotemia leads to a relative polyuria. The urinary volumes in Christiansen's cases support this view. Borst concluded that if by repeated hemorrhage or by operation, the patient develops shock, then diuresis and maximal urinary urea concentration both drop, and the blood urea value rises. In this same connection he found that the drop in urea clearance was more marked than the drop in blood pressure and hence was of greater value as a prognostic sign. During the stage of blood dilution the excretion of sodium chloride was low, and if sodium chloride was administered to the patient, the plasma content of this substance rose far above normal.

Sucic and Meyler independently reported their own observations on azotemia in gastro-intestinal hemorrhage. Sucic noted in his patients a progressive increase of blood urea following severe hemorrhage into the gastro-intestinal tract in 6 out of the 7 patients whom he mentions in his report.

Meyler noted high blood urea values in his patients and although he felt that death was not caused directly by the uremia that nevertheless the uremia was a serious complication.

In 1935, Ingegnò reported 41 cases of hemorrhage due to peptic ulcer.

From this summary, it would appear that the maximum blood urea values were present on the third and fourth days after the hemorrhage. In two patients a persistence of high blood urea indicated a continued hemorrhage and presaged the patient's death.

In 1936, Alsted reported a group of 26 cases of gastro-intestinal hemorrhage. In 15 of these he noted that the average rise in blood urea was highest on the second day with a rapid fall by the eighth and tenth days followed by a slow fall to normal in 26 days.

In 1938, Bookless encountered 13 cases in which there was a raised blood urea value following hematemesis and melena.

From these observations it becomes quite clear that an elevated blood urea value frequently accompanies gastro-intestinal hemorrhage. It now becomes important to determine, if possible, the cause of this blood urea rise.

As to the cause of this elevation of the blood urea in gastro-intestinal hemorrhage, Christiansen stated that the azotemia is a symptom of intoxication arising from absorption of toxic substances that form by bacterial decomposition of the blood in the gastro-intesti-

nal tract. This intoxication is further aggravated by demineralization from excessive flushing of the organism by water.

Borst states that the azotemia is induced by the increased formation of urea from blood in the gastro-intestinal tract and to an increased protein catabolism after cessation of the hemorrhage.

In discussion of his views, Sucic, on the basis of his observations, feels that the rise in blood urea is not brought about by the digestion of the blood, nor to a moderate loss of blood by hemorrhage and further is probably not due to marked and sudden loss in sodium chloride and fluid from the body. He thinks that the rise in urea is probably caused by a deficient urinary excretion and some increase in catabolism.

Meyler maintains that the azotemia is caused by the large quantities of protein which are destroyed and that the kidneys are not equal to the task of excreting the excess nitrogen. He also feels that there is an insufficient amount of fluid for adequate disposal of this excess nitrogen.

Ingegnò considers that the rise in blood urea is caused by a number of factors which includes sudden loss of blood, shock, dehydration, and absorption of blood nitrogen liberated in the gastro-intestinal tract.

Alsted says that the increase in the blood urea is due to the reduction in renal function caused by low blood pressure. In lighter hemorrhage, he considers that the rise is due to resorption of blood from the gastro-intestinal tract and a dehydration of the tissues.

Bookless considers that the rise in blood urea after hemorrhage is mainly produced by an increased breakdown of tissue protein, a process rapidly increased by sudden loss of blood and later maintained or further accelerated by dehydration.

## SUMMARY

We have presented a summary of the work which has been done on the subject of extrarenal azotemia. This state may be produced by either an increased nitrogen catabolism or deficient nitrogen excretion.

It is fairly well proved that a state of extrarenal azotemia exists in many patients in whom there is acute gastro-intestinal hemorrhage. We have presented the essential facts in such a case and have reviewed the similar experience of other authors.

The maximum rise in the blood urea in these patients apparently takes place between the second and the fourth day after the onset of the hemorrhage with a gradual return to normal thereafter.

We have summarized the many theories as to the cause of this urea rise, and conclude that the number of theories offer proof of our lack of knowledge.

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# Extrarenal Azotemia in Gastro-Intestinal Hemorrhage

## (II) Experimental Observations

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AS stated in the previous paper, azotemia of extrarenal origin occurs in many patients after severe gastro-intestinal hemorrhage. Unfortunately, there is no agreement among writers as to the cause of the rise in blood urea, and very little experimental investigation has been carried out to clarify the situation.

We wanted to learn if extrarenal azotemia could be produced in experimental animals by bleeding them or feeding them blood, or bleeding and then feeding blood. If the blood urea could thereby be made to rise, we wanted to know when it would rise and how long this rise would persist. Would there be any relationship between the extent of the hemorrhage and the height of the rise, and if a rise occurred, why did it come.

In the experiments now to be described, we usually removed blood from the heart and placed it in the gastro-intestinal tract by stomach tube. While we realize that this single large loss of blood and the feeding of blood does not compare strictly with spontaneous gastric hemorrhage, it nevertheless does resemble it a good deal.

### TECHNIC

Healthy dogs, which weighed from 5 to 15 kilograms, were chosen. The animals were given 0.5 gr. of morphine sulphate subcutaneously. As soon as narcosis became evident 50 cc. of blood was withdrawn from the heart. This was added to a 2.5 per cent solution of sodium citrate in the ratio of 20 cc. of anticoagulant to each 100 cc. of blood. A small amount of blood (4 to 8 cc.) was preserved with potassium oxalate for use in making chemical determinations. In the experiments where blood was fed, this was accomplished by means of a stomach tube. Approximately two hours after the onset of the experiment, 5 to 10 cc. of blood was withdrawn from the jugular vein for chemical determinations. In experiment I, the determinations were repeated at intervals of one to four hours for five days until it was determined that the reaction under study was complete within the first three days. In the remainder of the experiments, samples were withdrawn at critical times as determined from experiment I. The animals were all allowed water as they desired it, and in experiments I through VI they were given their usual morning feeding.\* The method of determining the amounts of blood to be withdrawn and fed was arbitrarily selected as the number of cubic centimeters of blood required to match numerically a given per cent of the body weight. That is, if a dog weighed 10 kilograms, then 1 per cent of blood would be equal to 100 cc.; 2 per cent equal to 200 cc., etc.

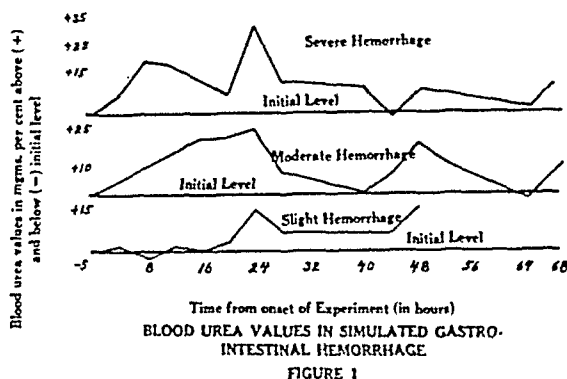
Method of chemical examination: The methods for

chemical determinations used were as follows: 1. Blood urea—van Slyke and Plazin. 2. Blood non-protein nitrogen—Folin and Wu. 3. Plasma chloride—Osterberg-Schmidt. 4. Hematocrit—Wintrobe.

### EXPERIMENT I

Thirty-seven dogs were used. These were separated into three groups: the first included thirteen dogs, and each of the other two groups included twelve dogs. Each series of dogs were bled and fed amounts of blood representing slight, moderate, and severe hemorrhage.

In the first group of thirteen dogs there was a slight hemorrhage, representing from 0.5 to 1.0 per cent of the body weight (average 0.76 per cent for the entire group). Similarly in the second group of twelve dogs, a moderate hemorrhage was considered to be 1 per cent to 1.6 per cent of the body weight in cubic centi-



meters of blood (1.28 per cent for the entire group), and from the third group with severe hemorrhage amounts of over 1.6 per cent were removed (average of 2.38 per cent for the entire group).

In Fig. 1 are shown the average blood urea values for these three groups of dogs at each of the stated intervals. The values are expressed as milligrams of urea per hundred cubic centimeters of blood greater (plus) or less (minus) than the initial value.

Comment: The blood urea values in all three groups have certain characteristics in common: (1) all reached a high peak value twenty-four hours after the bleeding and feeding, (2) this sharp rise was followed by a drop in urea values in from forty to

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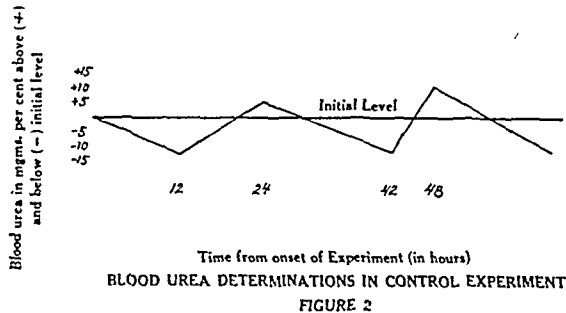
\*Red Heart kibbled dry dog food was used.  
Submitted October 16, 1939.

forty-four hours after the onset, (3) there followed a second and less pronounced rise at forty-four to forty-eight hours and (4) there was a gradual return to initial levels. The blood urea varied with the size and extent of the hemorrhage.

### EXPERIMENT II

As a control, a group of five dogs was treated in exactly the same manner as in experiment I except that no blood was withdrawn from the heart nor was any blood fed to them.

Blood for chemical determination was obtained at the most informative intervals as judged by experiment I. Thus, immediately after and then twelve, twenty-four, forty-two, forty-eight and sixty-four hours after the beginning of the experiment, we obtained blood for chemical determinations. This practice was followed in all subsequent experiments. In this group of dogs we likewise determined the urea ratio, plasma chloride, and hematocrit values, (Fig. 2)



*Comment:* A rise in blood urea values occurred within a few hours after the morning feeding. This was followed by a drop in the urea value which reached a low point several hours preceding the subsequent intake of food. This rise was not nearly so great as that which occurred when the dogs were bled and fed an amount of blood representing slight hemorrhage, as in experiment I. The urea ratio and plasma chloride values did not change significantly.

The hematocrit values fell slightly, possibly due to the withdrawal of blood for chemical determinations.

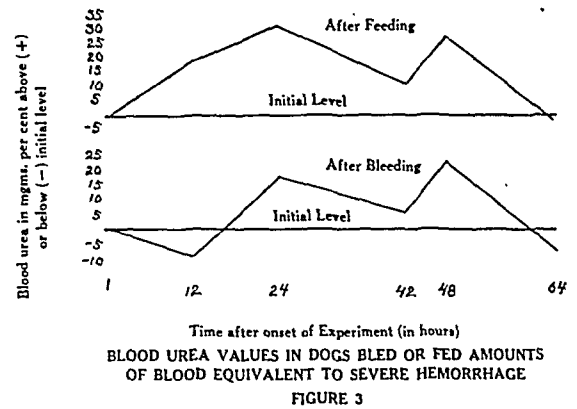
### EXPERIMENT III

On the basis of the information gained from experiment I, we decided to bleed one group of animals and feed blood to a second group in order that the various factors at play in this blood urea value rise might be dissociated.

Accordingly, by the technic already described, twelve dogs were bled amounts of blood equivalent to severe hemorrhage. For the entire group this averaged 2.29 per cent of the body weight or an amount but slightly lower than the previous comparable group in experiment I. Another twelve dogs were each fed this blood by stomach tube in similar amounts which in this group averaged 2.27 per cent of the body weight.

Except for this difference, the animals were all handled in a manner similar to the first experiment.

The average blood urea values obtained may be seen in Fig. 3.



*Comment:* From a comparison of these two sets of figures we can say that: (1) in the dogs which were bled there was an immediate drop in the urea value followed by a sharp rise at twenty-four hours; (2) while in the dogs which were fed blood, there not only was a rise in the urea value at twelve hours, but the urea value continued to rise until at twenty-four hours its value was almost twice that of the group which was bled; (3) in both groups there was a sharp fall at forty-two hours and in both a second rise at forty-eight hours followed by a return to normal levels at sixty-four hours; (4) it was notable that the secondary rise in the group which lost blood was almost as great as the group fed blood.

It appears from this that the loss of large amounts of blood will produce a rise in blood urea values. The simple feeding of blood will also produce a rise in blood urea values, but this is greater in extent. Further, the rise in blood urea after blood loss is most pronounced at the end of forty-eight hours, while after blood feeding, the peak of blood urea values comes in from twelve to twenty-four hours.

### EXPERIMENT IV

Six dogs were bled as before of an amount of blood which averaged 2.29 per cent of the body weight of each.

*Comment:* From the hematocrit determinations (Wintrobe), it was immediately apparent that after hemorrhage, dilution of the remaining cells soon takes place. This dilution reached its maximum at the end of forty-two hours from which time on release of cells into the blood stream, equalled or exceeded any further dilution. The period of greatest dilution of the blood occurred at the same time as the marked drop in blood urea values (forty-two hours).

### EXPERIMENT V

In a manner similar to experiment IV, 7 dogs were each fed an amount of blood equivalent to 2.27 per cent of the body weight.

*Comment:* In this experiment there was a rise in the hematocrit value representing a concentration of the blood. This took place in twelve hours and was immediately followed by a gradual slight dilution

which reached a maximum point at forty-two hours. From this time on there was no marked change. As might be expected, there was no great drop in erythrocyte content.

### EXPERIMENT VI

In order to determine whether temporary renal impairment might be responsible for the rise in urea values, some form of renal function test must be utilized. Accordingly the urea ratio was chosen because of its simplicity and apparent accuracy (4). We selected at random 2 dogs from each of the two groups.

*Comment:* There was no marked change in any of the values from the initial levels. In the dogs which lost blood there was a slight lowering of the urea ratio (increased function) at twelve hours, but this was immediately restored to levels above the initial state. These slightly high levels were maintained throughout. The high urea ratios perhaps indicate some crowding of renal function, but the values do not seem high enough to indicate real failure.

### EXPERIMENT VII

We considered that feeding our animals every morning, as is our usual custom, would undoubtedly cause some rise in the blood urea values. Accordingly, we conducted a series of experiments on fasting animals comparable to those of the preceding experiments.

In our fasting control group, we used 6 dogs; in the group which we bled there were 5 dogs (bled average of 2.43 per cent) and in the group fed blood there were 6 dogs (fed average of 2.52 per cent).

We estimated the blood urea, chloride, urea ratio and hematocrit values at regular stated intervals as in the previous experiments.

The information gained from this experiment is shown on the accompanying figure. (Fig. 5)

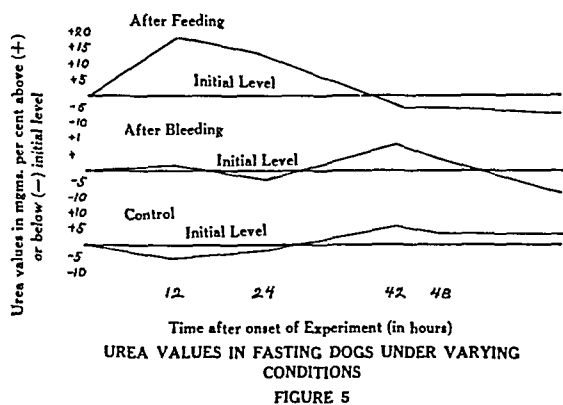


FIGURE 5

*Comment:* In the dogs fed blood, there was a rise in the blood urea for twelve to twenty-four hours after the beginning of the experiment. At the same time there was a slight decrease in renal function indicated by the high urea ratio and a temporary relative increase in circulating erythrocytes. In the next twelve hours there was a dilution of the blood and a drop of the urea value. In this experiment there was no secondary rise and this makes one assume that in our

earlier experiments the delayed rise was due to ingestion of food.

In the animals which were bled, the urea rise was present at forty-two to forty-eight hours, but was not so marked as in the previous comparable experiment. Here again the regular feeding probably had accentuated the rise which occurs with hemorrhage.

The plasma chloride values were not significantly altered.

### DISCUSSION

In answer to the questions stated in our introduction, we may say that a state of extrarenal azotemia can be produced in dogs by bleeding them from the heart and by refeeding this blood by stomach tube. Furthermore, either the loss of blood or the feeding of it will produce an azotemia. With feeding alone, the peak came after from twelve to twenty-four hours. With bleeding it came at 48 hours.

In any event, whether the azotemia is produced by bleeding and feeding or by either method singly, the rise persists over a period of only twelve hours at the most, after which the blood urea values return to normal. Adding the regular diet accentuates rises.

In simulated gastro-intestinal hemorrhage the blood urea value reaches a higher level as the hemorrhage is more extensive. The highest values in our experiments were reached with amounts representing massive hemorrhage.

What is the mechanism for this urea rise after the loss of blood or after ingestion of blood, or both? Is the rise due to a temporary renal shutdown?

From a study of the urea ratio values, we can probably eliminate renal failure as a factor. Other evidence may be deduced indirectly. First, if renal failure is to be produced by hemorrhage, the maximum urea rise should probably occur at the time of greatest shock. Actually, the renal function was improved at this time. Our dogs recovered from the effects of massive hemorrhage rapidly and in a few hours appeared to feel as well as ever. Further, in these animals the rise in blood urea did not occur soon after the hemorrhage but only after from forty-four to forty-eight hours.

Is the urea rise due to an increase in protein catabolism? In the animals which were bled there is an immediate drop in both the hematocrit and urea values. The drop is undoubtedly due to a loss of circulating urea as well as to a dilution of the blood. However, the urea values then begin to rise while the hematocrit value continues to fall. The urea rise must almost certainly be due to the liberation from tissues of urea or potential urea stores. This reaction reaches a maximum height within the first forty-four to forty-eight hours, and is undoubtedly accentuated by feeding of a diet high in protein. After forty-eight hours there seems to be no further need for the urea (maintenance of colloid balance?) and at the same time the hematocrit values tend to level off indicating the point of maximum blood dilution.

According to Taylor and Lewis the nitrogen catabolism is accelerated and blood non-protein nitrogen may rise to a moderate extent after severe hemorrhage. This effect is apparently not due to the anemia because the elevation of non-protein nitrogen disappears before the blood elements are returned to normal. Our findings were essentially similar. We

were unable to support Buell's contention that an early rise in blood urea occurs after hemorrhage.

At the time of maximal blood dilution the sources of urea are exhausted and protein catabolism probably increases to restore the loss of this substance to normal levels. At the same time the hematocrit values tend to rise.

In the animals which were fed blood almost the opposite reaction occurs. There is a sustained urea rise which continues for twenty-four hours in spite of the fact that the hematocrit value falls after twelve hours. The fall in hematocrit value must indicate an attempt to diminish the high blood urea content by dilution with tissue fluids. What explanation is adequate in this instance? The actually ingested urea, if it were immediately absorbed should raise the blood urea level only from 6 to 8 mgms. per cent. The actual rise is 30 mgms. per cent or more. Undoubtedly protein digestion products may account for some of this rise, but it also seems logical to account for a part of the rise by an increase in protein catabolism. Recall the urea ratio values which are at the highest point at and just preceding this time. This might be interpreted as an attempt to remove urea through increased renal excretion, the elevated ratio being evidence of this crowding of renal function.

The delayed blood urea rise which occurs at forty-eight hours is accompanied by a slight rise in hematocrit values. This may concurrently be the effect of one of several things: absorption of protein split products, dehydration or increased protein catabolism. Against dehydration as the cause is the fact that at no time were these animals deprived of water, the slight hematocrit value rise may be some evidence of hemoconcentration due to dehydration, although it is very slight. If the rise in urea values were due to increased protein catabolism the rise probably should be greater in extent and last for a longer period of time. Then, too, the blood in the gastro-intestinal tract should furnish sufficient nourishment to forestall any necessity for increased catabolism. Absorption of split products of the ingested protein remains then as the most logical source for the extra urea. This rise is apparently accentuated by feeding because it is not present in fasting dogs. Against this source we must suppose that protein cleavage is sustained so long as there is digestible material in the intestinal tract. Therefore, the rise one would expect to be produced by this means would be a long, slow rise with a long, slow fall to normal. The slow fall should occur as the digestible material decreases in amount.

The plasma chloride values did not become significantly altered in any of these experiments. This appears to be evidence that hypochloremia per se has nothing to do with the azotemia of gastro-intestinal hemorrhage.

Finally, in no instance did any animal assume the clinical picture of uremia. The small amounts of blood

withdrawn at intervals for chemical examination did not appear sufficient to influence the results.

## CONCLUSIONS

We have attempted in dogs to parallel the effects of spontaneous gastro-intestinal hemorrhage by removing blood from the heart and placing it in the gastro-intestinal tract with a stomach tube.

An extrarenal azotemia can be produced which is characterized by two rises in the blood urea value, the first at twelve to twenty-four hours, and the second forty-two to forty-eight hours after the beginning of the experiment.

When fasting and non-fasting animals are used and when one group loses blood only and the other is fed blood only, we can dissociate this double curve into its component factors. Thus, the initial rise is produced by the feeding of blood and the secondary rise is due to loss of blood. The initial rise takes place within twelve to twenty-four hours and the secondary rise forty-two to forty-eight hours after the onset of the experiment. Both elevated values fall within a very few hours (five to twelve) and both are accentuated if food of a high protein content is allowed.

Plasma chloride, and urea ratio determination values were probably not significantly altered in any experiment.

The blood urea rise is due to several factors, first to assimilation of the ingested protein and digestion products of the whole blood in the gastro-intestinal tract, and second to an increase in protein catabolism.

Hypochloremia, hemoconcentration and dehydration played no significant role in this form of extrarenal azotemia due to simulated gastric hemorrhage.

From what we have found in dogs, it is reasonable to assume that restoration of blood volume and efforts aimed to diminish the increase in protein catabolism should constitute ideal medical management of bleeding peptic ulcers. For the restoration of blood volume, drip transfusions could well be used. To diminish the increase in protein catabolism, one might give fluids with glucose and sodium chloride. We are attempting now to see if this actually does help.

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## The Maximal Acidity of the Intestinal Contents During Digestion\*

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THE presence of moderately strong acid in the small intestine affects a number of gastro-intestinal functions, for example, the activity of the pyloric sphincter, gastric peristalsis and gastric secretion and the secretion of pancreatic juice. This fact has led to speculation regarding the possible role of intestinal acidity in the regulation of these functions. It is obvious that regulation by such means is possible only when the acidity of the intestinal contents is great enough to act as a stimulus to the regulatory mechanism. Hence, knowledge of the *maximal* acidity of the intestinal contents and the *minimal* acidity required to stimulate the various regulatory mechanisms is necessary for an intelligent discussion of the problem of "acid control."

There have been many studies of the pH of the intestinal contents (1, 2, 3, 4) but, so far as we know, no prior attempt has been made to ascertain the maximal acidity that may be present under normal circumstances during digestion. The present study was undertaken for the purpose of supplying this information. The minimal acidity required to affect some of the functions that may be subject to acid control is also being investigated and the results will be reported later.

### METHODS

Twenty-six experiments were performed on five dogs provided with cannulated gastric and duodenal fistulas in a manner previously described (5). The animals were in good physical condition and were thoroughly accustomed to the laboratory and to the necessary manipulations. Food was given once daily and the animal to be studied was brought to the laboratory before being fed—i. e. approximately 24 hours after the last meal. Sampling tubes were inserted and the dog was fed its regular meal of raw beef, after which samples of the gastric and intestinal contents were taken at intervals from the body of the stomach, the pyloric antrum, the first part of the duodenum and from the lower duodenum or upper jejunum. Raw meat was used because it is known to increase the acidity of the intestinal contents more than carbohydrate or fat (4, 6). The meat used on the day of the experiment was selected for freedom from fat and all visible fat was removed.

The samples from the pyloric antrum and from the upper duodenum were collected through two tubes connected with one another by means of a short piece of thread. They were passed via the gastric and duodenal cannulas into the stomach and duodenum and placed so that their connected ends were only a few mm. from the pylorus and the connecting thread was within the pyloric orifice (Fig. 1). There were openings in the sides of these tubes placed so as to be not more than

2 cm. from the pylorus. Another tube was inserted through the gastric cannula into the body of the stomach and a fourth was passed through the duodenal cannula into the lower duodenum or upper jejunum to a point between 30 and 40 cm. from the pylorus. The cannulas were closed with rubber stoppers provided with holes for the exit of the various collecting tubes.

Samples from the upper duodenum and pyloric antrum were taken every 5 or 10 minutes during the first half hour after feeding and, thereafter, every 30 minutes and from the other levels at irregular intervals. Observations were generally made over a 4 hour period; a few experiments were terminated at the end of 3 hours and some were continued for 5 hours. In a majority of the experiments the pH determinations were made with a gold, quinhydrone electrode; more

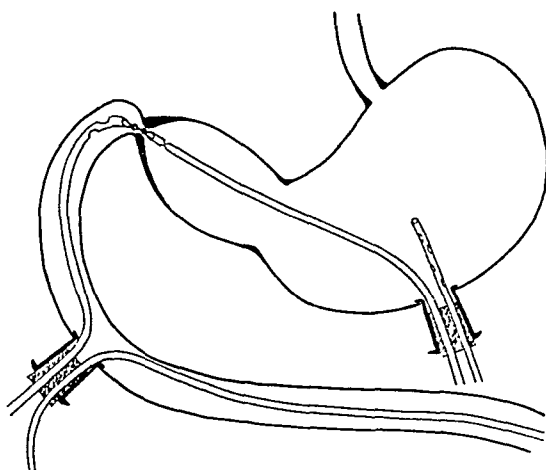


Fig. 1. Diagram of the stomach and upper small intestine showing the approximate location of the cannulated fistulas and the manner of arranging the sampling tubes.

recently an L. and N. pH indicator with a glass electrode was used. Determinations were made on all samples as soon as collected to avoid changes due to the progress of digestion and loss of  $\text{CO}_2$ .

### RESULTS

*The first part of the duodenum.* The reaction of each of the 210 samples from the upper duodenum was, with 11 exceptions, within the range from pH 3.0 to pH 4.8, inclusive. The exceptions were distributed as follows: 1 each at pH 2.4, 2.5, 2.8, 5.0, and 5.2; 3 at pH 5.4; 1 each at pH 5.7, 6.6, and 7.1. Samples that were collected during the first 10 minutes after feeding are not included in this analysis because they are thought to be more nearly representative of the fasting than of the digesting state. They were less acid than the others. The frequency distribution of the in-

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cluded results, minus some of those listed as exceptional, is shown graphically in Fig. 2.

*Lower duodenum and upper jejunum.* Results obtained on the 58 samples collected from this region are illustrated in the lower graph of Fig. 3. They are probably not numerous enough to give a characteristic curve but they suggest that the acidity at this level was less than that in the first part of the duodenum by

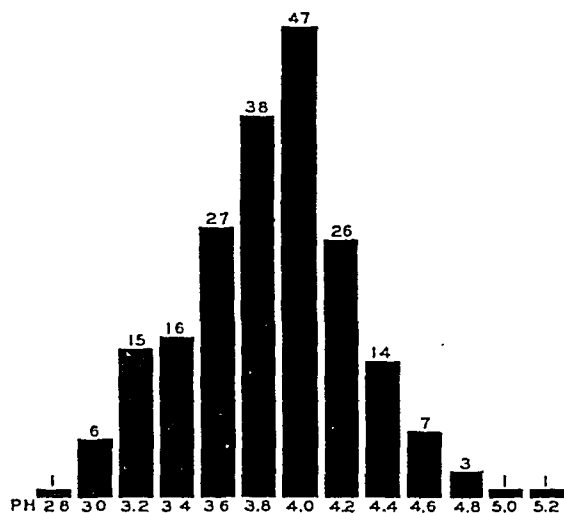


Fig. 2. Distribution of samples collected from the first part of the duodenum with respect to pH. The height of each column is proportional to the number of samples having the reaction indicated in pH units at the bottom of the column. The number of samples is indicated at the top of each column.

approximately one pH unit. The significant range appears to be between pH 4.2 and pH 5.8, inclusive.

Also shown in Fig. 3 (upper graph) are results obtained in a previous study (6) in which the samples were collected from a point in the duodenum between 15 and 20 cm. from the pylorus, under conditions otherwise identical with those maintained during the present study. As was to be expected, the acidity in this region was intermediate between that of the first part of the duodenum and that of the lowest portion.

*Stomach.* Observations of the pH of the gastric contents were made primarily as a check on the effect of the experimental conditions on gastric acidity. Samples obtained from the body of the stomach generally had a pH between 1.5 and 2.0, well within the accepted normal range for the gastric contents. Samples obtained from the pyloric antrum were definitely less acid and for that reason it seemed worth while to make a sufficient number of observations to establish the normal acidity of the contents of this part of the stomach under the conditions of these experiments.

The results are shown graphically in Fig. 4. Most of the samples in which the pH was less than 2.0 were obtained during the first hour after feeding. During the greater part of the period of observation the reaction of the antral contents ranged between pH 2.0 and pH 3.0.

## DISCUSSION

Two important considerations bearing on the possibility that acid in the intestine may serve as a regulator of gastro-intestinal functions are the acidity of

the gastric contents as they leave the stomach and the length of time required for their neutralization within the duodenum. Probably the prevalent opinion is that the acidity of the chyme is little altered until it enters the duodenum where it is partially neutralized but only after a time interval during which the acid may act as a stimulus to various regulatory mechanisms. These experiments do not support this view. On the contrary, they indicate that the greater part of the gastric acid is neutralized in the pyloric antrum and that the acid which remains fails to appear in full strength, even momentarily, in the duodenal contents. The consistent difference in the pH of samples collected simultaneously from just above and just below the pylorus is so striking as to suggest the existence of a special mechanism for the further neutralization of the gastric contents the moment they enter the duodenum.

Such a mechanism is, perhaps, to be found in the so called "receptive relaxation" of the duodenum first described by Joseph and Meltzer (7). Thomas and Crider (8) found that the "receptive relaxation," i.e., the inhibition of duodenal tone and activity which is associated in time with the exit of chyme from the stomach affects only the first six or eight inches of the duodenum and is most pronounced in the immediate vicinity of the pylorus. Such selective inhibition must cause pressure differences within the duodenum which would force the contents to flow into the region of greatest relaxation and, therefore, to accumulate on the duodenal side of the pylorus just at the moment that the gastric chyme makes its exit from the stomach. Thus the chyme would always be poured

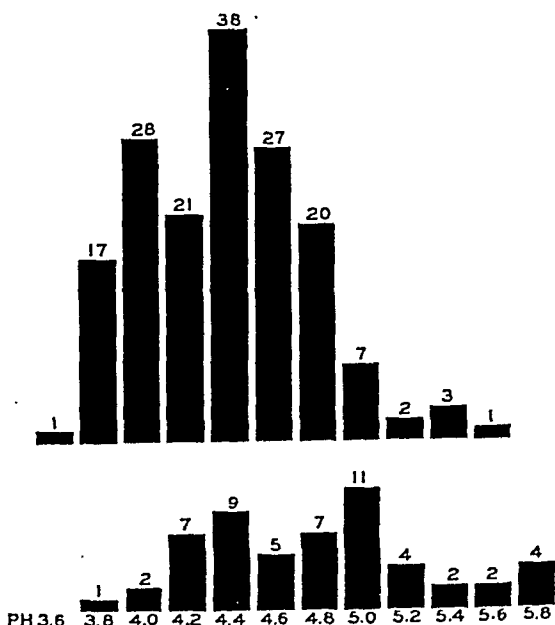


Fig. 3. Distribution of samples collected from the duodenum and upper jejunum with respect to pH illustrated as in Fig. 2. *Upper graph*—samples collected from a point between 15 and 20 cm. from the pylorus (Thomas and Crider (6)). *Lower graph*—samples collected from a point between 30 and 40 cm. from the pylorus. Both graphs are constructed on the pH scale given at the bottom of the lower graph.

directly into a relatively great volume of the heavily buffered duodenal contents and be instantly diluted and partially neutralized. If further study should justify this logic and prove its applicability to the human, an interesting field for speculation would be opened regarding the possibility of failure of the mechanism under pathological conditions, e.g. duodenal spasm, and the relation of such failure to the etiology of duodenal ulcer.

Whether the acidity actually found in the duodenal contents is adequate to modify any function remains to be determined. Preliminary experiments (9) have indicated that it is inadequate to affect gastric peristalsis but difficulties have been encountered owing to

differences in the effectiveness of different acids at the same pH and further study will be necessary.

These experiments do not exclude the possibility of the occasional occurrence of acidity in excess of pH 3.0 in the duodenum. Higher acidities have been observed when the stomach was empty (3) presumably as a result of the passage of fasting gastric secretion into the duodenum and on rare occasions during digestion. There is little reason to doubt that on such occasions at least the various "acid control" mechanisms are active and useful to the organism.

### SUMMARY

1. Under conditions designed to produce the maximal normal acidity in the intestinal contents during digestion, the acidity in the duodenum near the pylorus rarely exceeded pH 3.0 and was generally near pH 4.0. The acidity was less in other parts of the duodenum and upper jejunum.

2. The contents of the pyloric antrum near the pylorus were consistently less acid than the contents of the body of the stomach and generally had a reaction between pH 2.0 and pH 3.0.

3. The suggestion is made that the "receptive relaxation" of the duodenum, by causing an accumulation of duodenal contents in the vicinity of the pylorus at the moment of exit of gastric contents, facilitates the quick dilution and partial neutralization of the chyme.

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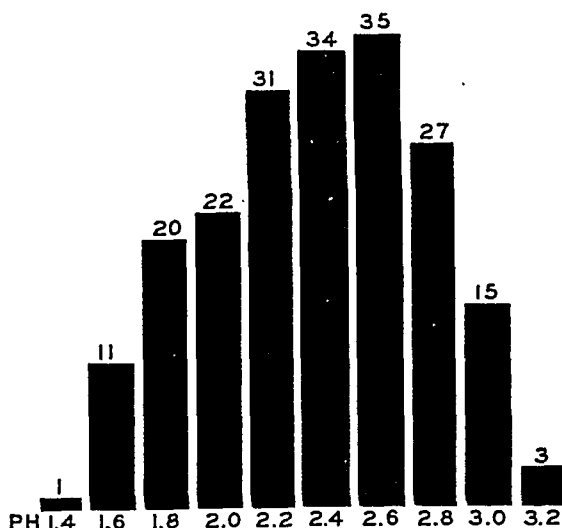


Fig. 4. Distribution of samples collected from the pyloric antrum with respect to pH illustrated as in Fig. 2.

## Acidity Modification Therapy in Peptic Ulcer\*

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**R**EDUCTION of gastric acidity is at present still considered an important factor in the management of patients with peptic ulcer. For this purpose, the clinician has at his disposal a number of substances called antacids. Due to the fact that there is quite a divergence of opinion about the efficacy of these various antacids, we thought it pertinent to investigate the antacid properties of four currently used substances in the treatment of peptic ulcer: (1) Sippy No. 1 powder (calcium carbonate one part and sodium

bicarbonate three parts); (2) Amphojel (as representative of the colloidal aluminum hydroxide group); (3) a neutralized Karaya Gum† (representing the mucilagenous group); and (4) Acid-bismuth mixture (a mixture of bismuth subnitrate and dilute nitric acid).‡

One hundred active peptic ulcer cases were studied. Each fasting patient was given a dry Rehfuß tube to swallow, and the fasting stomach contents were aspirated and tested for free and total acidity. The amount of juice, its characteristics and admixtures were noted. Usually, 5 to 50 cc. was obtained. Some patients showed a retention up to 200 or more cubic centimeters.

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Foot Note: Numerous illustrations which were omitted from this article because of lack of space will appear in the reprints—Editor.

†Prepared for us by Parke, Davis & Company.

‡Bismuth subnitrate 45.0, Dilute Nitric acid 60.0, water to make 240.0.



After emptying the fasting stomach, the patients were given a test meal which in Group A consisted of 250 cc. of 7% alcohol, and in Group B of 4 arrowroot crackers and 250 cc. of water. Aspirations were performed every 15 minutes for 2 hours. The free and total acid values for each specimen were determined with the usual reagents. All determinations were done by the same person throughout this study.

Each patient was subjected to these fractional test meal studies on five successive days. In Group A, the patients were given the alcohol test meal for the first two days and the acid curves obtained were considered as the control. On the third, fourth and fifth day, the antacid to be studied was given immediately following the test meal, and the aspirations done every 15 minutes.

In Group B, the patients were given the arrowroot cracker meal, and the first day acid curve was used as control. Furthermore, these patients were given the antacid in two installments. The first dose was given as in Group A, while the second dose was given immediately after the aspiration of the fourth specimen. Thus the neutralizing effect of antacids given at close intervals could be observed. The dose of the different antacids used was the same in both groups: It was one heaping teaspoonful of Sippy powder on one day and one heaping teaspoonful of Karaya Gum, 8 cc. of the amphotel, and 8 cc. of acid-bismuth mixture on the other days.

During the period of intubation, the patients were allowed to be up and about, to converse, read "bland" literature, or write. Smoking was prohibited. The patients were told not to swallow any saliva or posterior nasal secretion. The gastric contents were syphoned off each 15 minutes. In some patients nothing could be aspirated after 90 or 105 minutes, which was interpreted as rapid emptying time.

The results of these studies, with little difference between Group A and B, were as follows: All four antacids frequently produced relief of pain, but they often failed to produce a constant lowering of the free acidity. The acidity was lower in only 11% of the cases after Karaya; in 15% after Sippy No. 1 powder; in 23% after amphotel; and in 18% after acid-bismuth mixture. It was higher than the control acidity in 21%, 25%, 16% and 14% respectively. Sippy No. 1 powder produced complete neutralization for the duration of the test in 10% of the cases and amphotel in 8%. The Sippy No. 1 powder, moreover, produced very marked fluctuations and greatest rise in the acidity.

### DISCUSSION

The fact that relief of pain is frequently obtained without definite or constant neutralization of acidity

*Stiller's solution for free acidity. Phenolphthalein for total acidity.*

demonstrates conclusively that antacid action is not the sole factor responsible for the relief. From our observations and from reports in the literature, it seems that relief can most probably be explained on a lessening of gastric tension (1). The latter occurs whenever anything is placed into the stomach, a fact which would probably explain the beneficial results in the ulcer patient, from the use of frequent meals alone.

The fact that the various agents we have tried had essentially the same antacid effect does not mean that they are all equivalent so far as therapeutic value is concerned. From our studies, it appears that one or another of the various agents discussed, all of which have similar symptomatic value, may at times be more conducive to the healing of an ulcer.

From the results of fractional aspirations, it is evident that, in order to prevent the irritating effect of fluctuations in acidity, Sippy powder would have to be given at almost half-hour intervals, a regimen which may be impractical for a long time and dangerous because of changes in the acid-base balance (2, 3, 4, 5, 6).

These studies support our clinical observation that patients would go along best on that medication which during the test gave either continuously lower acidity or the least fluctuations in acidity in either direction. Thus, in many instances good clinical results were noted even when the medication showed a somewhat higher acidity curve, but when there were no marked fluctuations in the gastric acidity. It appears therefore, that the stomach tries to maintain a certain status quo of its chemistry, and that anything that markedly upsets this state is irritating and disturbing to the stomach (7). In the treatment of an ulcer, therefore, we should not concentrate our efforts upon the reduction of acidity merely, since acidity is not the most important link (8) in the chain of symptoms of an ulcer patient. It seems justified to stress the point that ulcer therapy is not based solely on decreasing the gastric acidity (8).

### CONCLUSIONS

1. All of these agents have given symptomatic relief in a large percentage of cases, without producing a uniform and constant reduction in the gastric acidity.
2. Therefore, the relief of the pain must have been secured in a different manner than simply by means of an antacid action.
3. We have no right to speak of an antacid action in connection with any one of the four agents tested.

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## Secretary Studies in Whole Stomachs The Determination of Phenol Red in Gastric Contents\*

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THE use of phenol red in gastric analysis, for the purpose of determining quantitatively the proportion of residual test-meal present in a sample of gastric contents, was first introduced by Gorham (1923). Since then this pigment has been used as a dilution indicator more extensively than any other substance. A method for the quantitative estimation of phenol red in the presence of bile and protein suspensions has been described by Wilhelmj and his co-workers (1933, 1936). On preliminary investigation of this method we found it to be unsatisfactory for the following reasons: (1) It frequently requires the application of a subjective color correction in advance of a colorimetric determination. This correction involves the addition of a variable volume of phenol red-pipic acid solution to the colorimetric standard, in order to adjust the tint of the latter to that of the unknown. (2) When concerned with bile-containing specimens, the use of this correction procedure necessitates the preparation of a different colorimetric standard for each such sample. (3) In the presence of dark green bile it may be impossible to make this correction at all. (4) Finally, although the authors stated that the procedure yields quite accurate results, no data were cited to indicate its quantitative reliability.

In order to eliminate the need for this subjective correction, we have developed a simple quantitative procedure for the simultaneous removal of protein and bile pigment without loss of phenol red. The procedure, with but minor modifications, has been in use in our laboratory for well over a year, during which period it has continued to give us very satisfactory results. At no time has it failed to remove bile pigment completely from the specimen. Likewise, Shay and his associates (1938) have found it satisfactory in their studies. We are therefore presenting the following detailed report of the method and its reliability.

### PROCEDURE

The procedure is based on the Somogyi (1930) method for removal of blood proteins. In addition to the test-meal (which contains 40 mg. of phenol red per liter), the required reagents are finely powdered CaO (50 mesh), NaOH solution (0.5 N), ZnSO<sub>4</sub> solution

(0.3 N), and Na<sub>3</sub>PO<sub>4</sub> solution (0.5 N). Successive steps in the determination are as follows:

1. The gastric specimen, containing phenol red, must first be centrifuged for about 10 minutes at 2500-3000 R.P.M. This serves also to remove all coarse particles preliminary to acidity and chloride determinations.

2. To 5 ml. of the centrifuged specimen in a 15 ml. centrifuge tube add enough of the CaO (with stirring) to neutralize the gastric HCl and to make the solution distinctly alkaline to phenol red. Excess CaO does not interfere with the subsequent procedure.

3. Add one ml. of the NaOH solution, mix, and then add 2 ml. of ZnSO<sub>4</sub> solution with shaking. Keep the tube stoppered with a rubber cap until after the next step.

4. Let stand for 15 minutes and then centrifuge for 10 minutes.

5. Transfer 5 ml. of the supernatant fluid to another 15 ml. centrifuge tube; add 3 ml. of Na<sub>3</sub>PO<sub>4</sub> solution to precipitate the excess Zn and simultaneously to adjust the pH to a value suitable for colorimetry (circa 12).

6. Centrifuge again for 10 minutes and filter carefully with suction through a small Hirsch funnel, discarding the first few drops of filtrate which may contain traces of solid. Shay employs decantation instead of filtration at this stage; in our experience, however, the latter is more reliable. This filtrate is now ready for colorimetry.

7. As a standard of reference, use a portion of the original test-meal which has been subjected to the same preparatory treatment as the unknowns. Following the final adjustment of pH by the addition of Na<sub>3</sub>PO<sub>4</sub> and filtration, this solution can be diluted quantitatively so that its phenol red concentration will conform to the rule that the colorimeter readings for standard and unknown must never differ by more than  $\pm 50$  per cent of each other. However, if the required precision need be no better than 1 per cent of the initial test-meal concentration, a single reference solution, made by four-fold dilution of a portion of the test-meal and subjected to the above procedure, can be used for comparison with any unknown independently of its concentration. Evidence in justification of this is presented below.

8. In the case of solutions of very low phenol red concentration, difficulty may be encountered in match-

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A preliminary report of this work was presented in the *Proc. Soc. Exp. Biol. Med.*, 36, 568, 1937.  
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ing the colors because of their low intensity. This difficulty can be overcome by the method of Wilhelmj and Baca (1938), who mix a convenient volume of such an unknown with an equal volume of the original test-meal, and then use a 5 ml. portion of this mixture instead of the unknown itself for the determination. The value for phenol red concentration in the original specimen is then equal to twice the observed value, minus the concentration in the test-meal. In our laboratory we have found that the use of a green Wratten color filter (No. D) obviates the need for this mixing procedure—particularly since our maximum concentration of phenol red is higher than Wilhelmj's (40 mg. per liter as against 15). Likewise, as Shay has pointed out, the use of such a filter increases the ease of color-matching throughout the entire concentration range, and we now use it routinely in conjunction with an electric bulb of suitable luminosity.

9. The concentration of phenol red in the specimen is calculated in the usual way from the known value of the *undiluted* test-meal, which is determined in duplicate like any of the unknown specimens. If  $R_u$  and  $R_t$  represent the colorimeter scale readings for unknown and test-meal respectively, and  $P_u$  and  $P_t$  represent the corresponding concentrations of phenol red, then

$$P_u = P_t \times \frac{R_t}{R_u}$$

If it be desired to determine directly the proportion of test-meal ( $ft$ ) present in each fraction, this can be calculated by the equation

$$ft = \frac{R_t}{R_u}$$

### RELIABILITY OF THE METHOD

In order to determine the reliability of the foregoing method, we performed an extensive series of determinations on various solutions of known composition, and studied the frequency distribution of the individual errors (expressed in mg. per liter) of the series. In these solutions the phenol red concentration varied from 40 to 0.5 mg. per liter. The indicator was mixed with either egg albumen, gastric secretion obtained from canine pouches, Liebig's extract, or human stomach contents of varying characteristics (i.e., high or low mucus content, extremes of acidity, and bile content varying from thick dark green to complete absence). From the statistical summary of this frequency distribution presented in Table I, it is evident that the errors are uniformly distributed about zero; the mean (with regard to sign) is + 0.006, with a standard deviation of  $\pm 0.02$ , and the mode is - 0.016 (all in terms of mg. per liter). Furthermore, although the range is - 0.6 to + 0.9, only four of the 108 values are greater than  $\pm 0.4$ . Hence, except for an occasional excessively large error, such as would probably be detected in a pair of duplicate determinations, the maximum error may be taken as 0.4 mg. per liter or 1 per cent of the initial concentration of phenol red in the test-meal. In analytical practice the precision of a method is best evaluated in terms of the standard deviation (or the probable error). For these 108 errors the standard deviation is  $\pm 0.22$  mg. per liter, and in future discussions of the precision of the

phenol red method we shall use this value as a measure of its reliability.<sup>1</sup>

Recently Wilhelmj and Baca (1938) compared the reliability of our method with that of their own, by performing duplicate determinations with both methods on each of a series of gastric specimens of *unknown* phenol red content. They concluded that "the two methods are about equally reliable," provided that specimens of low phenol red concentration be mixed with an equal volume of test-meal before starting the determination by either procedure—as described above in paragraph 8 of the section on PROCEDURE. In this comparison, "equal reliability" was inferred from

TABLE I

*Errors in phenol red determinations. A statistical summary of the frequency distribution of the errors (E) in a series of single determinations on a variety of phenol red mixtures which contain gastric secretion, human stomach contents, bile, Liebig's extract, etc. (E = calculated concentration—observed concentration)*

Statistical Constant	Value	Comment
1. Number of determinations	108	Actual concentrations of phenol red were in the range 0.5-40.0 mg./liter.
2. Standard deviation $\sigma$	$\pm 0.22$ mg./liter	This constant is used as a measure of the reliability of the analytical procedure.
3. Mean (E) error	+ 0.006 mg./liter	This constant represents the mean of the entire distribution of errors, with due regard to sign.
4. Standard error of E ( $\sigma_E$ )	$\pm 0.021$ mg./liter	
5. Mode	- 0.016	Of the 108 values, 29 were 0.0 and 42 were $\pm 0.1$ mg./liter.
6. Range of error	- 0.6 to + 0.9 mg./liter	Of the 108 values, only 4 were greater than $\pm 0.4$ mg./liter.

the agreement of two such values to within  $\pm 4$  per cent of the initial concentration of phenol red in the test-meal—such agreement having been obtained in 57 out of a total of 65 specimens (i.e., 88 per cent of all those studied). Actually, such a comparison of two methods tells nothing about the reliability of either, unless the two observed concentration values can be compared with a third, "true" value which is known

<sup>1</sup>These observations were made with the aid of a new Klett colorimeter. Prolonged use of this instrument, however, has suggested that this standard deviation may be increased somewhat by the use of an old colorimeter. Since Shay (1938) has confirmed our estimates of reliability with the use of a photo-electric colorimeter, we are now investigating the possible adaptation of such an instrument for our own purposes.

A value of 0.22 mg./liter (0.55% of the test-meal concentration) for the precision measure of this method may impress the reader as being very low for any procedure involving the use of an ordinary colorimeter. Several facts of statistical significance must be borne in mind, however. In the first place, the entire range of error (-0.6 to +0.9) corresponds to a maximum error of 2.3% of the test-meal concentration, which value is more in harmony with common experience. The  $\sigma$ -value, on the other hand, indicates a range of error within which only about two-thirds of all the errors may be expected to fall; a range of error equal to twice  $\sigma$  will include approximately 95% of all observable errors; three  $\sigma$  will include about 99.7%, etc. Furthermore, the  $\sigma$ -value is given as per cent of the test-meal concentration (40 mg./liter), but if it were expressed in relation to the individual observed concentrations these percentage values will be as high as 44% for the lowest concentration value included in the distribution (i.e., 0.22 divided by 0.5).

for each specimen independently of the analyses. No such true values were available in the experiments of Wilhelmj and Baca because of the nature of their specimens. Since, in our laboratory as well as in that of Shay, our method rarely results in an error of more than 1 per cent of the initial concentration ( $\pm 0.4$  mg. per liter in 40), it must be inferred either that Wilhelmj's method is considerably less reliable than ours or else that his technicians have not been able to take full advantage of our technique. The latter possibility is suggested also by the following facts: (1) Wilhelmj and Baca report the occasional failure of the  $\text{Zn}(\text{OH})_2$  to remove all bile pigment, and (2) they report considerable difficulty in reading the more dilute phenol red solutions treated by our method, unless these solutions had previously been mixed with an equal volume of test-meal in order to increase the measurable concentration of phenol red. Neither of these difficulties has been encountered in this laboratory.

The importance of utilizing an analytical method which is good to within 1 per cent of the initial concentration of phenol red will become manifest from a study of the way in which the analytical errors are compounded in the course of a gastric analysis based on the dilution indicator technique. This problem will be discussed at length in the next paper of this series.

### DISCUSSION

*The pH requisite for colorimetry.* It is generally known that phenol red loses its color rapidly in a strongly alkalized solution (Lubs and Acree, 1916; Thiel, 1929). Thus, in the presence of 1.0 N NaOH, we have found that a measurable amount of color is lost during the first half hour, whereas in 0.1 N and 0.01 N NaOH the color is stable for at least six hours. On the other hand, if the pH be not high enough, the color will be incompletely developed in the first place because of incomplete conversion to the salt form. According to the pH-dissociation curve for phenol red (Clark, 1938) the indicator develops its maximum color at about pH 10; we have confirmed this by a colorimetric comparison of three phenol red solutions of identical concentration and of pH values of 10, 11 and 12 respectively. Hence, the final pH must be no less than 10, and not much greater than 12. Since the pH of the  $\text{Na}_3\text{PO}_4$  solution is in the neighborhood of 12, this reagent serves simultaneously to precipitate excess Zn and to adjust the final pH to a value suitable for colorimetry.

*The colorimetric standard of reference.* In preparing the reference solution, the use of the original test-meal, rather than a pure solution of phenol red, is chiefly a matter of convenience. In the case of a Liebig's extract test-meal, however, it has the particular advantage that color differences which arise with a standard containing only phenol red will be minimized with a standard prepared from the test-meal itself, because of the presence of the colored extractives in both colorimeter cups. Such a standard, if undiluted, would correspond to an initial pre-treatment concentration of 40 mg. per liter—the highest value likely to be encountered in a series of determinations. In order to adhere to the accepted principle (Peters and Van Slyke, 1932) that the concentration of standard should never deviate from that of the unknown by more than  $\pm 50$  per cent, the reference solution must be diluted to an extent determined by each specimen. The resultant precision should be of the

order of  $\pm 1$  or 2 per cent of the observed concentration value for each specimen. If, however, a precision of  $\pm 1$  per cent of the original test-meal concentration—corresponding to an absolute value of  $\pm 0.4$  mg. per liter and independent of the individual concentrations—is all that is required, then it suffices to dilute the test-meal 4 times before subjecting it to the Zn treatment and to use this standard throughout the series of determinations. Table II demonstrates the agreement between calculated and observed concentration values obtained when such a single colorimetric standard (corresponding to a pre-treatment concentration of 10 mg. per liter) was employed throughout

TABLE II  
Agreement between observed and calculated values for phenol red concentration, when the colorimetric standard corresponded to a fixed value of 10 mg. per liter

Series	Ra	Pu (calc'd)	Pu (obs'd)	E
	mm.	mg./liter	mg./liter	mg./liter
I. Zinc treatment omitted	20.0	20.0	20.0	0
	20.0	18.0	17.9	+ 0.1
	20.0	16.0	16.1	— 0.1
	20.0	14.0	13.9	+ 0.1
	20.0	12.0	11.9	+ 0.1
	20.0	10.0	9.9	+ 0.1
	20.0	9.0	8.9	+ 0.1
	20.0	8.0	8.0	0
	20.0	7.0	7.1	— 0.1
	20.0	6.0	6.0	0
	20.0	5.0	5.0	0
	20.0	4.0	4.0	0
	20.0	3.0	3.0	0
	10.0	2.5	2.5	0
	10.0	2.0	2.0	0
	10.0	1.5	1.5	0
	5.0	1.0	1.0	0
Mean (without regard to sign)				0.04
II. Zinc treatment included	30.0	40.0	39.9	+ 0.1
	20.0	30.0	29.7	+ 0.3
	20.0	20.0	19.9	+ 0.1
	20.0	10.0	10.1	— 0.1
	20.0	8.0	8.0	0
	20.0	6.0	6.1	— 0.1
	15.0	4.0	4.2	— 0.2
	10.0	3.0	3.3	— 0.3
	5.0	2.0	2.1	— 0.1
	5.0	1.5	1.6	— 0.1
	3.0	1.0	1.2	— 0.2
Mean (without regard to sign)				0.15

### COLUMN HEADINGS

Ra—Fixed colorimeter reading (left scale).  
Pu—Concentration of phenol red in unknown (right cup)—Mean of two determinations.  
E—Error = Pu (calc'd) — Pu (obs'd).

### COMPOSITION OF SPECIMENS

Series I—Test-meal consists of 40 mg. of phenol red in water. Solutions for analysis are mixtures of test-meal and water.  
Series II—Test-meal consists of 40 mg. of phenol red and 20 mg. of Liebig's extract in fasting stomach contents. Solutions for analysis are mixtures of test-meal and stomach contents.

the experiment. In the first series, solutions were used which contained only phenol red and were not subjected to the Zn treatment. In the second series of this table, all the solutions were prepared from a test-meal which contained fasting stomach contents, phenol red (40 mg. per liter), and Liebig's extract (20 mg. per liter), by diluting the test-meal with additional quantities of stomach contents; furthermore, all solutions of the series were subjected to the Zn precipitation treatment before being read. From the last column of the table, it is manifest that the discrepancy between observed and calculated values (i.e., the error) never exceeded  $\pm 0.3$  mg. per liter.

### CONCLUSION

A method has been described for the quantitative determination of phenol red concentration in specimens of stomach contents which contain Liebig's extract, bile, mucin, and other protein substances—such as would be obtained in the course of a gastric analysis in which phenol red is used as a dilution indicator. All interfering substances are removed adequately for colorimetry, without appreciable loss of the indicator. The reliability of the method was established on a series of individual determinations on 108 mixed

specimens, prepared with various proportions of a test-meal containing 40 mg. of phenol red per liter. The standard deviation of this distribution was  $\pm 0.22$  mg. per liter. The mean error (with due regard to sign) was  $+ 0.006$  and the mode was  $- 0.016$  mg. per liter. Although the range of errors was  $- 0.6$  to  $+ 0.9$ , only four of the 108 error values were greater than  $\pm 0.4$ , or one per cent of the concentration of phenol red in the test-meal.

The authors wish to express their thanks to Dr. Harry Shay for the improvements in technique suggested by him and also for his confirmation of the quantitative reliability of the procedure.

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## The Use of Phenol Red as a Dilution Indicator in Gastric Analysis\*

By

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THE importance attached to the dilution indicator technique in gastric analysis is manifested by the fact that efforts in this direction were first reported more than 40 years ago in a paper by Mathieu (1896). Since then numerous attempts have been made to use such a technique for the purpose of estimating the proportions of test-meal and secretion in a gastric analysis specimen, and for the correction of acid and chloride concentrations for dilution by the test-meal. The difficulties inherent in the development of the dilution indicator method, and particularly the difficulty in finding a suitable substance to be used as the indicator, have sometimes seemed almost insurmountable. Not until Wilhelmj and his co-workers adopted the use of phenol red (phenolsulfonphthalein) for this purpose—originally introduced by Gorham (1923) ten years before—did it appear as if these difficulties had finally been overcome. Their development of the technique and their numerous reports of its persistent use since 1933 for the investigation of various problems in the gastric physiology of dogs have been well summarized in two articles in this *Journal* (Wilhelmj, Finegan and Hill, 1937; Wilhelmj, 1937).

In view of the inadequacy of phenolphthalein as a

dilution indicator, (Hollander, Penner and Saltzman, 1937), and the success which Wilhelmj appeared to have with phenol red, we decided to adapt the dilution indicator technique to a study of the secretory curves on human subjects, with and without apparent gastric disease. A preliminary investigation of the possible loss of phenol red in the human subject (both normal and pathological) by gastric absorption, chemical change, or preferential staining of the gastric mucosa, demonstrated the absence of such losses of the pigment, thus enhancing the reliability of its use for our purpose (Penner, Hollander and Saltzman, 1938). Accordingly we performed a series of such analyses using several kinds of test-meals. The resultant acidity and chloride curves, uncorrected for test-meal dilution, were in no way different from what we anticipated from analyses with gruel (without phenol red) as test-meal. The corrected curves, however, yielded values for the concentration of chloride in the secretion which in most instances were startlingly high. Since a minute investigation of the nature and causes of these high values is impossible on human subjects, it was decided to study the phenomenon on dogs instead. In the present report, therefore, we present our observations on human subjects and indicate the possible reasons for these peculiar results. Subsequently, we shall report on our similar experiences with dogs and

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the technique we have employed to overcome the difficulties which these experiences presented.

### METHODS

The gastric analyses were performed with but minor variations in the usual fractional technique. With the subject in the fasting state, a Rehfuß tube was passed and the fasting contents were aspirated completely. The stomach was then washed by introducing 100 ml. of the test-meal and reaspirating as quickly as possible; a specimen of this wash fluid was retained for analysis. Following this, 300 ml. of the test-meal was introduced; at 15 minute intervals thereafter, the entire stomach contents were removed and mixed, a 15

minute interval was used in the analytical procedure described in the previous article (Hollander and Penner, 1940). From the concentration values so obtained, we calculated the proportions of test-meal and of secreted fluid in each gastric sample; also the actual concentrations of chloride and acid in the secretion contained in each gastric sample; also the actual concentrations of chloride and acid in the secretion contained in each such sample (i.e., the concentrations *corrected for dilution by the test-meal*).

The calculations were performed by means of formulae (1), (2) and (3), in which:

$C_o$  = the concentration of chloride (or acid) in any

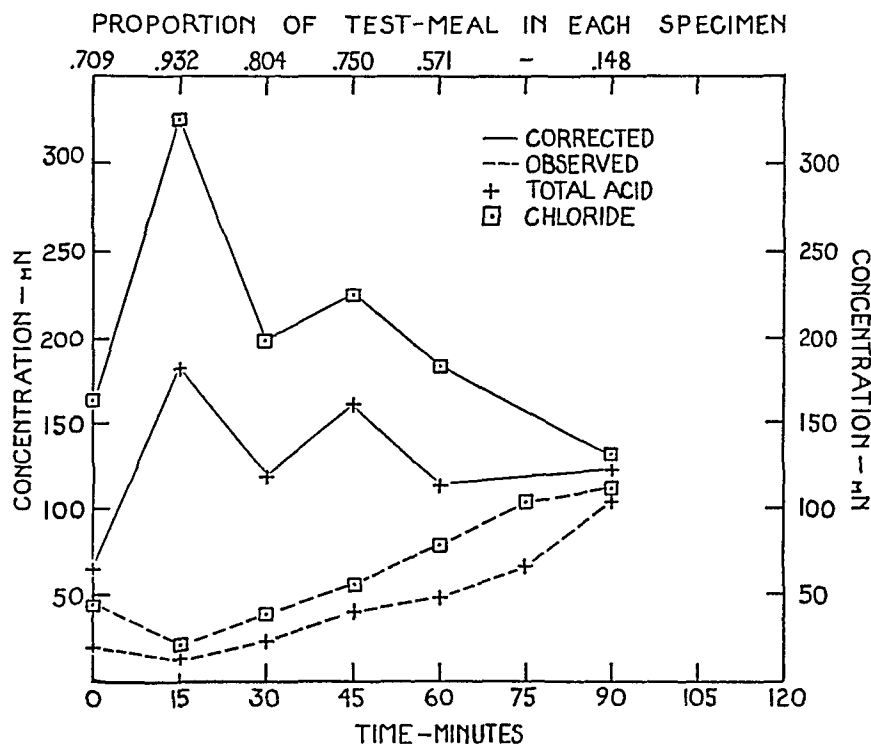


Fig. 1. Gastric analysis (total acidity and total chloride) curves with and without correction for dilution by the test-meal. Experiment K-14. Subject: M. S. Test-meal: Alcohol = 7%, phenol red = 40 mg. per liter volume = 300 ml.

ml. portion was retained for analysis, and the remainder was returned to the stomach. This procedure, which has the advantage of yielding truly representative specimens of the entire gastric contents, was continued until no more fluid could be obtained. Four different test-meals were employed—water, 3.5 per cent alcohol, 7 per cent alcohol, and 6.7 mg. of caffeine per liter—each containing 40 mg. of phenol red per liter. In general, two fractional analyses were performed with each test-meal on each of 3 subjects, making a total of 26 series in all.

Each specimen was analyzed for free and total acidity, total chloride concentration, and phenol red concentration. For the two former we employed our usual semi-micro methods; for the phenol red determi-

gastric sample (hereafter called the *observed concentration*).

$C_s$  = the concentration of chloride (or acid) corrected for test-meal dilution, i.e. the calculated concentration in the mixed secretion without test-meal (hereafter called the *corrected concentration*).

$P_o$  = the concentration of phenol red in the gastric sample (hereafter called the *observed concentration of phenol red*).

$P_t$  = the concentration of phenol red in the test-meal (called the *initial concentration of phenol red*).

$f_t$  = the proportion by volume of test-meal in the gastric sample.

$f_s$  = the proportion by volume of mixed secretion in the gastric sample.

Then, from the observed values for Co, Po, and Pt we have:\*

$$ft = \frac{Po}{Pt} \quad (1)$$

$$fs = 1 - ft = \frac{Pt - Po}{Pt} \quad (2)$$

$$Cs = \frac{Co}{fs} = \frac{Co Pt}{Pt - Po} \quad (3)$$

If the test-meal contains titratable acid or chloride, formula (3) for Cs becomes somewhat more complicated, but this does not apply in the present situation.

The three subjects for this study were all male workers in our laboratory, who presented no symptoms referable to the digestive tract and were in excellent general health for the duration of the experiments.

### OBSERVATIONS

In general the curves for the observed concentrations were not particularly different from what one might expect in the course of any ordinary fractional analysis. In the case of the series with water test-meals, the specimens recovered were fewer in number and smaller in size than with the other test-meals—particularly the alcohol meal. Hence it was not possible to determine the phenol red concentrations on any extensive series of specimens with the water meal unless histamine or some similar stimulus were used in conjunction with it.

The results of a single illustrative experiment with a 7 per cent alcohol test-meal are presented in Fig. 1. The broken lines represent the *observed concentrations* of total acid and chloride; the *corrected concentrations* are represented by the unbroken lines. The proportion of test-meal (ft) in each specimen is indicated at the top of the graph. Although the broken line graphs are both reasonably normal, the observer is struck by the fact that one of the 5 corrected acidity values and 4 of the corresponding chloride values are well above 165 mN—a value which, as we have previously shown, corresponds to the concentration of HCl in pure parietal secretion in dogs, and which represents the approximate concentration of HCl and NaCl solutions which are isotonic with the blood and tissue fluids. This observation is in no way fortuitous, for of the 49 specimens in which we were able to determine the phenol red concentration as well as acidity and chloride values, 6 (12 per cent) gave corrected acidity values greater than 165 and 28 (57 per cent) gave corrected chloride concentrations above this physiological limit. The highest values obtained were 209 mN for total acidity (Experiment K-23) and 750 mN for total chloride (Experiment K-33); the latter corresponds to a solution which is more than 4 times the isosmotic concentration of blood.

Now, the occurrence of such hypertonic values can be ascribed to either or both of two reasons: (1) there may actually exist in the unoperated stomach a secretion, the total osmotic concentration of which is so high as to be four or more times that of blood; and (2) absorption of fluid may occur through the gastric

mucosa, thus increasing the apparent concentration of chloride and acid in the secretion as it is measured by this method. So far as we know today, no such hypertonic secretion passes into the gastric cavity from the stomach mucosa itself or through either gastric orifice. On the other hand, there already is considerable evidence in the literature which demonstrates the ability of the gastric mucosa to absorb water, although some investigators have maintained that such absorption does not occur. It may be objected that the volume-rate of absorption is so low, compared with the total volume of secretion and test-meal present in the gastric cavity, that this factor is quantitatively negligible. The argument is fallacious, however, for it can be shown that the mathematical process employed to convert *observed concentration* of chloride or acid to *corrected concentration*—represented by equation (3)—applies the entire burden of this absorption to the secretion and not at all to the test-meal, and thus magnifies its influence in this regard.

In order to demonstrate how this happens, without going into a detailed mathematical proof of it, let us suppose that 100 cc. of a chloride-free test-meal (concentration of phenol red equal to 40 mg. per liter) is introduced into an empty stomach for a defined period of observation, and that during this period 10 ml. of parietal fluid (concentration of HCl equal to 165 mN) is secreted and 5 ml. of water absorbed. On complete withdrawal of the mixture at the end of this period we will have the following:

Vo = volume of gastric sample = 105 ml.

Po = observed concentration of phenol red = 38.1 mg. per liter

Co = observed concentration of chloride = 15.7 mN

Pt = initial concentration of phenol red (in the test-meal) = 40 mg. per liter.

By calculation, using equations (1), (2) and (3), we have:

ft = proportion of test-meal in the gastric sample = 0.952

fs = proportion of secretion in the gastric sample = 0.048

Cs = concentration of chloride in the secretion = 330 mN

Note that this value for Cs is double the actual concentration. However, if water absorption is assumed not to occur at all we will have:

Vo = 110 ml.

Po = 36.36 mg. per liter

Co = 15.0 mN

and by calculation

ft = 0.909

fs = 0.091

Cs = 165 mN

In this case, the value for Cs is exactly equal to the true value for the secretion. Hence, an absorption of 5 ml. of fluid from a mixture of 100 ml. of test-meal and 10 ml. of secretion would make the apparent volume of secretion equal to 5 ml. (i.e. 10 - 5) and so make all the *corrected concentration* values (i.e., the apparent values for concentration of chloride and acid in the secretion) just double the actual values for the secretion as it was elaborated by the mucosa.

A careful search of the data published by Wilhelmj and his associates from 1933 to the present, revealed that such hypertonic values were encountered in their dog experiments also—both with whole stomach

\*The mathematical bases for these formulae will be published elsewhere, together with a discussion of the analytical errors inherent in the dilution indicator technique (Hollander and Glickstein, 1940).

pouches and with unoperated dogs on which the fractional analysis technique was employed (Wilhelmj, O'Brien and Hill, 1936). In two instances the value for total chloride in the secretion was well over 300 mN. Without adducing any supporting evidence, these investigators have accepted such hypertonic chloride values as evidence of the occurrence of fluid absorption by the stomach, but they have neglected the influence of this absorption on their corrected concentrations and therefore on their final conclusions. If absorption be the true explanation for these high values, it follows that all such estimations of acid and chloride concentrations in the total gastric secretion, the non-acid secretion or "extra fluid," the acid fluid, or the fluid regurgitated from the duodenum, must all contain serious errors. The same holds true for estimations of the corresponding volumes as they are performed by Wilhelmj, Neigus and Hill (1934), nor does there seem to be any way of correcting these concentration and volume values for such fluid loss, inasmuch as the volume-rate of absorption must be highly variable and generally unknown. On the other hand, estimations of total amounts of acid and chloride (in contradistinction to concentrations) are not influenced by water absorption per se, unless the water loss be accompanied by absorption of acid or neutral chloride.

Thus we are faced with what may prove to be an insurmountable complication in the application of the dilution indicator technique, a complication which invalidates many of the conclusions already drawn from data obtained by this method. Hence, it becomes necessary to determine whether the foregoing observations are really due to fluid absorption. If it be so, it is essential that we discover what steps if any can be taken to eliminate, or minimize the magnitude of this absorption. Because of the great number of gastric analyses which must be performed in the course of such an investigation and the consequent strain on the subjects, we have interrupted the present study on man in order to continue it on dogs with unoperated stomachs. It may be that the present difficulties can be satisfactorily resolved by suitable modifications in technique, and if such experiments demonstrate this

to be so we plan to make use of the modified procedure in a continuation of the study of patients with various types of gastric disorder.

## SUMMARY AND CONCLUSION

An attempt was made to apply the dilution indicator technique with phenol red to fractional gastric analysis in man, using various test-meals. When correction was made for dilution of the parietal cell secretion by the test-meal, it was found that a significant number of observations yielded corrected values for both total acid and total chloride which were well above 165 mN. Several of these corrected chloride values were even greater than three times the isotonic concentration (i.e., 495 mN). Similar values have been noted by Wilhelmj and his co-workers in their experiments with dogs. Since in dogs it is known that the parietal cell secretion is isotonic with blood and tissue fluids, and all evidence points to the same situation in man, we feel that the hypertonic corrected values for acidity and total chloride may be the result of water absorption from the stomach. This circumstance, and the fact that the degree of water absorption is unpredictable, introduce an error into the dilution indicator technique which we do not yet know how to eliminate. These facts render clinical application of the dilution indicator technique of doubtful value at the present time, and further investigation is now being carried on with dogs in an effort to establish the source of these abnormally high values and, if possible, to find a way of correcting the errors resulting from their occurrence.

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# Psychic Gastric Secretion in Man\*

By

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**F**OLLOWING the work of Pavlov (1) on conditioned reflexes in animals a good many studies have been made of human "psychic" secretion. The usual procedure has been to allow the subject to see, smell or chew attractive foods and to measure the gastric secretion in comparison with a previous control observation. In some cases unpleasant stimuli such as bad odors have been used and one writer claims to have exposed his patients to sensations of "disgust, sadness, fear, rage and pleasure" (2) to determine the effect on gastric secretion. None of these experi-

ments has been carried out with satisfactory methods and at most one can conclude that various stimuli may be followed by increase or by diminution in the flow of juice. The older literature is reviewed by Carlson (3) and by Babkin (4) and among recent papers one may refer to those of Schaverin and Ostrovidowa (5), of Garin, Roment, Amic and Delorme (6), of Majus and Porges (7), of Wittkower (2), and of Necheles and Maskin (8). It is of interest that we have been unable to find any account of the effect on gastric secretion of suggestion of food without actual sight or smell of it except in a few patients under hypnosis. In the rather unsatisfactory reports of Wittkower (2)

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TABLE I

*Complete protocol of an experiment on psychic secretion. Patient A. L. (No. A58992). Diagnosis peptic ulcer of lesser curvature*

Specimen No.	cc. Juice Per 10-Min.	Character of Juice	Free HCl	Total Acid
1	60	Slightly bile tinged—fasting content	0	20
2	11	Mucoid with very faint bile tinge	0	20
3	8	Colorless fluid with some mucus	0	20
4	6	Colorless fluid—small amount of mucus	20	42
5	5	Colorless fluid—small amount of mucus	18	38
6	30	Colorless fluid—small amount of mucus	16	34

Comment: After removal of the fasting contents there was a small amount of continuous (basal) secretion. During period No. 6, the test period for psychic secretion, there was a prompt response to discussion of the patient's favorite foods with increase of volume from 5 cc. to 30 cc., but there was no increase in acidity.

and of Outerino and Jaso (9) the results were said to be variable. During the course of studies of basal gastric secretion we have been impressed by the active flow of juice which occurs in some people without any of the usual forms of test-meal or stimulus. It seemed desirable to supplement these observations by an exploration of the effect of psychological stimuli. It was thought that the results of a histamine test, a measurement of basal secretion and of "psychic secretion" would give a much more useful picture than either one alone. However the tests of psychic secretion were

of enough interest to justify a brief separate report, which is herewith presented.

## METHODS

The subjects were all at rest over night in the hospital. Under conditions as nearly "basal" as possible a small tube was introduced into the stomach and the juice obtained by continuous aspiration was collected over successive ten-minute periods. When the secretion had reached an approximately constant basal level the examiner, during a final ten-minute period, discussed with the patient the subject of his favorite foods and the methods of preparing and serving them. The volume and acidity of the juice during the control and test periods was compared. *The patients did not actually see, smell or taste food.*

## RESULTS

The general plan of the experiments is best brought out by a complete protocol of one case (see Table I), but all the observations may be summarized more briefly. (Table II, Chart 1). It is seen that in all cases except Nos. 10 and 6, in which the changes were within the limit of error, there was an increased flow of juice during the test period. Aside from Case 8, in which the extraordinary outpouring of secretion was an exception, the absolute increase varied from 6 cc. (Cases 9 and 11) to 24 cc. in Case 1. In proportion to the control period the flow was increased nearly 6 fold in Cases 8 and 1, and was tripled in Case 4, but as a rule the test period yielded less than double the control. The increase bore no definite relation to the control level. It is of interest that the changes in acidity were very much less striking than the accelerated rate of secretion. In Cases 2 and 13, and to a

TABLE II

*Summary of experiments on psychic secretion*

Case No.	Diagnosis	Control Period			Test Period			Remarks
		Volume cc.	Free HCl	Total Acid	Volume	Free HCl	Total Acid	
1	Peptic ulcer lesser curvature	5	18	38	30	16	34	Marked increase in volume but no definite change in acidity in spite of the low initial value.
2	Adhesions and duodenitis	9	36	48	24	61	72	Marked increase in both volume and acidity. Diagnosis verified at operation.
3	Duodenal ulcer	10	84	94	17	88	96	Moderate increase in volume without change in acidity.
4	Duodenal ulcer	10	114	120	29	102	112	Marked increase in volume without change in acidity.
5	Duodenal ulcer	11	62	98	20	60	102	Marked increase in volume without change in acidity.
6	Duodenal ulcer	13	90	98	16	98	106	Very slight increase in both acid and volume.
7	Duodenal ulcer	15	46	58	25	57	70	Moderate increase in both acid and volume.
8	Duodenal ulcer	15	26	46	85	48	60	Immense increase in volume; moderate increase in acidity.
9	Ulcer of intestine	15	73	82	21	80	90	Moderate increase in volume and acidity.
10	Gastric ulcer lesser curvature	16	0	10	14	0	10	No effects on volume or acid, but response to histamine.
11	Duodenal ulcer	17	51	67	24	51	71	Slight increase in volume; no definite change in acidity.
12	Duodenal ulcer	18	10	20	31	20	34	Moderate increase in volume; relatively large increase in acidity.
13	Duodenal ulcer	20	86	82	27	60	74	Moderate increase in volume; marked increase in acidity.
14	Duodenal ulcer	24	82	60	35	60	70	Marked increase in volume; slight increase in acidity.

TABLE III  
*Relation of age of patient to psychic secretion*

Case No.	Age	Control	Volume of Secretion (cc.) Test Period	Increase (cc.)
9	27	15	21	6
12	30	18	31	13
1	33	5	30	25
10	36	16	14	- 2
4	38	10	29	19
11	38	17	24	4
6	39	13	16	3
3	39	17	29	12
5	40	11	20	9
7	44	15	25	10
8	49	15	55	70
14	53	24	35	11
2	56	9	24	15
13	62	20	27	7

lesser extent in Cases 7, 8 and 12, there were moderate increases in total titratable acidity but for the most part the changes were negligible. In Cases 1 and 4 there was even a slight decrease. No correlation was made out between changes in volume of secretion and acidity. In Case 1 for example with marked increase in volume there is a slight fall in acid whereas in Case 13 with only slight increase in volume there is a considerable rise in titratable acidity. Finally it may be pointed out that in the few cases in which there was

a distinct rise in acidity the initial acid value during the control period was relatively low. Where the control value for titratable acidity was in the vicinity of 100 there was little further increase of acidity even when the flow increased on psychic stimulation. Case 10 deserves special mention. This concerned a woman with a large peptic ulcer of the stomach which was eventually proved to be benign. On several occasions there was no free HCl under basal conditions and psychic stimulation was not followed by increase of volume or acidity, despite the fact that she was psychologically a hypersensitive person. After a full dose of histamine volume of secretion rose from 16 cc. to 29 cc. and acid from 0 to free 28 and total 50.

It must be noted in connection with the variable results reported above that the stimulus could not be made identical in each case. In some instances the patient simply enumerated his favorite food, in others he told how he prepared certain dishes, etc., etc.

We have shown elsewhere that both the volume and acidity of gastric secretion decrease with advancing years if one averages the findings in large groups of people (10). It was necessary therefore to see whether age could explain variations in the present series. The results are tabulated from this standpoint in Table III and there is obviously no relation of psychic secretion to age.

It would be of interest to make a technical study of the psyche of these patients in the attempt to relate the secretory response to psychological make-up. Unfortunately this was not done in our cases.

#### SUMMARY

The effect of suggestion of palatable food on gastric secretion measured under controlled conditions is de-

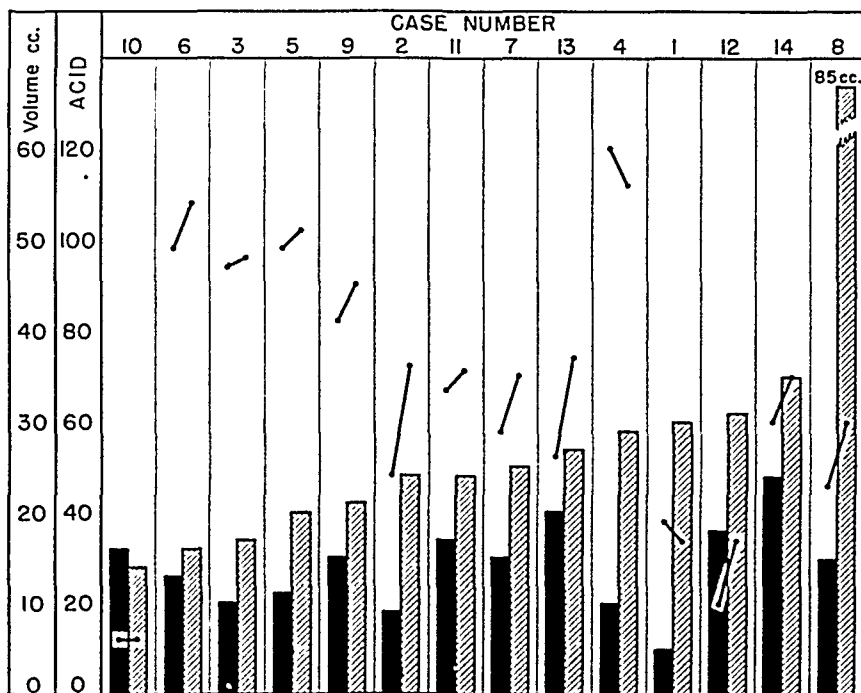


Chart 1. Psychic Gastric Secretion. (Lines = total acidity. Columns = volume of secretion; solid columns, control period; hatched, period of psychic stimulation).

scribed. The food was not actually seen, smelled or tasted. In 12 out of 14 subjects suggestion alone was followed by an accelerated flow of gastric juice. It was striking that the increase in volume of secretion was much more marked than the increase in acidity in contrast to histamine stimulation which normally has a notable effect on acidity. This may be explained by the fact that psychic stimulation is transmitted to the stomach by way of the vagus whereas histamine acts directly on the secretory cells.

The technique which we have described would lend itself equally well to study of the effect of unpleasant or indifferent stimuli and it would also be of interest

to correlate the subject's psychological make-up with his response to psychic stimulation.

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## Studies in Human Biliary Physiology\*

### IV. Comparative Effects of Orally Administered Olive Oil, Oleic Acid and Glycerine, With and Without Bile Salts, on Quantity of Bile Secretion

By

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IN a previous paper (1), we discussed the influence of the oral administration of whole bile on the rate and quantity of bile secretion of the normal liver. The choleric effect of whole bile, and more particularly bile salts has been ascertained beyond any question by many observers, prominent among whom have been Baldi (2), Paschkis (3), Rosenberg (4), Gumprecht (5), Pfaff and Balch (6), Doyon and Dufort (7), Joslin (8), Shaffer (9), Pitini and Fernandez (10), Boehm (11), and more recently, Okada (12), Foster, Hooper and Whipple (13), Specht (14), Mellanby (15), and Chabrol and Charronat (16). Within recent years, combinations of bile salts and oleic acid have been used rather extensively where choleric effects were desired, without much experimental background to ascertain the efficacy of such therapeutics. Okada (12) has shown that sodium oleate after ingestion exerted a stimulating effect on bile production, and Chabrol and Charronat (16) have demonstrated that oleic acid as well as sodium oleate when administered into the duodenum caused a marked choleresis. Finkelstein and Lipschutz (17) have attempted to show clinically that the feeding of bile salts and oleic acid by duodenal tube in humans resulted in a potentiation of the choleric effect over that produced by bile salts alone. It is difficult, however, to evaluate this work because of the great error encountered in measuring biliary secretion by means of duodenal tube collection. Moreover, these authors failed to take into consideration the cholagogue effect of such medication on the gall bladder. Co Tui (18) has more directly approached this problem by experimenting on dogs with a common duct fistula and a segregated gall bladder. He concluded that choleresis caused by a combination of relatively small doses of oleic acid and bile salts was

much more marked than would be expected from the sum of the effects of the same doses of bile salts and oleic acid administered separately.

The purpose of this study was to determine the effect of the commonly employed therapeutic doses of bile salts and oleic acid as well as aliquot quantities of olive oil and varying quantities of glycerine on a human with anatomic conditions analogous to those experimentally produced by Co Tui in dogs.

Procedure: The subject, a young cholecystectomized female with a total external biliary fistula, was placed on a standard hospital diet (P 75, C 200, F 100) for several days to bring her biliary output, collected by intubating the fistula, to constant values. During this period, none of the collected bile was re-fed orally. When this constant state was reached, the biliary secretion was measured hourly, beginning at 8 a.m. (breakfast at 7:30 a.m.) and continuing for fifteen hours (until 10 p.m.). Column 1, Table I, represents typical values found during such test periods. On the day following such a trial period, the subject was fed a gelatine capsule containing five grains of mixed bile salts (ordinary therapeutic dose) thirty minutes before each of the three meals of her standard diet. The bile was again collected hourly for fifteen hours. Column 2, Table I, represents typical values found during these test periods. The subject was then allowed to return to basic secretory values by feeding the standard diet and no oral bile. When this state was again reached, 3 cc. of oleic acid in gelatine capsules were fed thirty minutes before each of the three meals of the standard diet. Hourly specimens were again collected for fifteen hours. Column 3, Table I, represents typical values during such test periods. The subject was then again allowed to return to basic levels, following which 3 cc. of oleic acid and 5 grains of mixed bile salts were fed together thirty minutes

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TABLE I  
*Hourly flow of bile in cubic centimeters*

Time	1	2	3	4	5	6	7	8	9
8 A. M.	21.2	23.1	24.0	23.2	19.2	23.4	18.5	20.5	22.0
9	23.4	22.4	26.0	27.4	22.0	24.5	22.5	24.5	26.0
10	22.0	30.0	23.0	30.0	23.1	27.0	24.0	25.6	26.0
11	24.0	20.0	25.4	28.0	25.0	25.5	22.0	24.2	24.0
12	24.2	21.0	24.6	26.5	25.0	27.0	24.0	23.6	23.3
1 P. M.	21.4	29.0	21.1	34.2	30.0	25.0	22.0	27.0	26.1
2	22.6	28.0	23.0	27.4	22.1	22.6	24.0	25.5	22.8
3	21.8	24.0	25.8	27.0	22.2	22.0	24.0	24.0	27.0
4	23.1	27.0	26.2	34.2	22.1	25.0	22.4	27.2	26.0
5	26.8	25.0	25.4	36.0	22.0	26.5	28.0	26.0	25.0
6	22.6	30.0	23.6	32.5	25.1	27.2	26.0	26.0	25.0
7	21.8	29.0	22.6	24.0	22.2	26.6	25.0	26.0	22.6
8	25.4	21.5	29.1	27.0	25.0	25.5	25.2	25.0	25.0
9	23.2	28.0	22.8	26.2	22.2	23.0	25.0	25.0	25.0
10	21.2	23.6	23.0	29.1	21.0	25.0	21.0	25.2	20.2
Total	344.6	381.6	365.5	432.7	348.2	375.6	353.6	375.2	366.0

Column 1. On standard diet alone. Column 2. On standard diet plus five grains of bile salts with each meal. Column 3. On standard diet plus 3 cc. of oleic acid with each meal. Column 4. On standard diet plus 3 cc. of oleic acid and 5 grains of bile salts with each meal. Column 5. On standard diet plus 5 cc. of olive oil with each meal. Column 6. On standard diet plus 5 cc. of olive oil and 5 grains of bile salts with each meal. Column 7. On standard diet plus 1 cc. of glycerine with each meal. Column 8. On standard diet plus 1 cc. of glycerine and 5 grains of bile salts with each meal. Column 9. On standard diet plus 8 cc. of glycerine with each meal.

before each of the three meals of the standard diet. Hourly secretion was again recorded for fifteen hours. Column 4, Table I, represents typical values during such test periods. Following standardization of the patient on the test diet, an aliquot quantity of olive oil (5 cc.) was fed with each of the test meals and the bile again collected hourly. Column 5, Table I, represents such test values. Similar tests were done using the standard diet with the addition of 5 cc. of olive oil and 5 grains of bile salts to each of the three test meals. Column 6, Table I, represents typical values during such test periods. Inasmuch as we considered it impractical to use an aliquot quantity of glycerine (0.25 cc.), we increased this to 1 cc. which was added to each of the three standard meals after the subject

had been again been brought to basic values. No bile salts were added. Column 7, Table I, represents such test values. Similar experiments were conducted, adding both 1 cc. of glycerine and 5 grains of bile salts to each of the three meals of the test diet. Column 8, Table I, represents typical values obtained during this experiment. Finally, 3 cc. of glycerine alone was added to each of the meals of the test diet. Column 9, Table I, represents typical values of bile secretion under this regimen.

## DISCUSSION

Examination of Table II reveals that the addition of five grains of bile salts (ordinary therapeutic dose) to each of the three meals of the standard diet results in an increase of 11% in the quantity of bile secreted over that produced on the standard diet alone. The addition of oleic acid (3 cc.) to each of the three meals of the standard diet resulted in an increase of 6%. When both bile salts and oleic acid were given together with the standard diet, the increase in bile secretion was 26%, a value of 9% greater than would be expected were the bile salts and oleic acid to produce merely a summation effect (17%). The addition of an aliquot quantity of olive oil (5 cc. three times a day) to the standard diet produced no appreciable change (1%) in the quantity of bile secreted over that produced by the standard diet alone, whereas the addition of bile salts and olive oil produced a 9% increase, an effect which was directly due to the presence of the bile salts alone, inasmuch as this rise was of the same order as that found when bile salts alone were employed (11%). This observation is in accord with that of Kocour and Ivy (19) who found that olive oil in dogs is not a constantly reliable excitant of bile secretion except when fed once or twice after a period of fasting. Small doses of glycerine (1 cc. three times

TABLE II

*Comparison of quantitative bile secretion on standard diet and after the addition of bile salts, oleic acid, olive oil and glycerine*

Type of Feeding	Bile Secretion in cc.	Increase Over Diet Alone	Per Cent Increase Over Diet Alone
Standard diet alone	344.6		
Standard diet plus bile salts	381.6	37.0	11%
Standard diet plus oleic acid	365.5	20.9	6%
Standard diet plus bile salts and oleic acid	432.7	88.1	26%
Standard diet plus olive oil	348.2	3.6	1%
Standard diet plus olive oil and bile salts	375.6	31.0	9%
Standard diet plus glycerine (1 cc.)	353.6	9.0	3%
Standard diet plus 1 cc. glycerine and bile salts	375.2	30.6	9%
Standard diet plus glycerine (3 cc.)	366.0	21.4	6%

a day) produced a slight increase (3%) of bile secretion over that given by the standard diet alone, but this increase was enhanced (6%) by the use of larger quantities of glycerine (3 cc. three times a day). The addition of bile salts to the small doses (1 cc.) of glycerine did not produce any increase over that found when bile salts alone were used (9%). It is interesting to speculate on the failure of aliquot quantities of olive oil to produce any choleric effects. This may be due to either the non-digestion of the olive oil in the bile-free intestinal tract and the subsequent non-liberation of its component oleic acid and glycerine fractions or else, if such digestion does take place, the component oleic acid and glycerine fractions might conceivably arrive in the liver at any one time in quantities too small to produce any choleric effect.

### CONCLUSIONS

1. Oleic acid, orally administered in the usual therapeutic dose with an average mixed diet, stimulates the flow of liver bile in a cholecystectomized healthy human. Administered together with bile salts, oleic acid potentiates the choleric effect of the bile salts beyond the additive effects of each of these stimulating agents.

2. Olive oil, orally administered in amounts aliquot to the oleic acid used, neither stimulates the flow of liver bile when given with a mixed diet, nor does it potentiate the choleric effect of bile salts when fed

together with the latter. The failure of olive oil choleresis is consistently present with single or multiple olive oil feedings.

3. Glycerine, orally administered with an average mixed diet, seems to have a slight choleric effect but does not potentiate the choleric effect of added bile salts.

4. These findings suggest that the rate of digestion of the olive oil and the rate of absorption of its constituent oleic acid and glycerine and their concentration in the blood reaching the liver may be factors involved in the irregular choleric response or lack of response noted in the experimental study of the effect of olive oil on choleresis.

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## Some Remarks on Habitual Constipation and Related Nervous Disorders of the Rectum\*

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HABITUAL constipation is one of the most frequent disorders of the human body. It is, as far as I can learn, uncommon in animals except in dogs. It seems to me that the chief causal factor accounting for this fact is the habit of defecating at a certain time, mostly in the morning, mostly once a day only, and a suppressing, more or less unconsciously, the desire to empty the rectum at other times (1). Under normal conditions the whole reflex mechanism is trained in such a way that the mass movements of the colon take place at regular times and that therefore the feces enter the rectum and elicit the desire to defecate at these times only.

Such training of the reflex mechanism to act periodically with a high degree of precision can easily be frustrated by neglecting "to answer promptly the calls of nature" (Osler-Christian) and to respond to the sensation produced by a filled rectum. If it frequently occurs that the full rectum is not emptied by the voluntary act of defecation, then the normal sensation gets lost and a "torpor recti" results. This condition has been named "dyschezia" by Hurst. It is the common

opinion of the majority of experienced clinicians and physiologists that dyschezia is the most important factor causing habitual constipation. If the sensation aroused by the distended rectum has been neglected for a long period of time and therefore has faded, the rectum adapts itself to the increased fecal bulk and atony of the muscular bulk results.

The classification into the atonic and spastic varieties of habitual constipation has been largely abandoned because of the frequent combination of a spastic condition, particularly of the descending colon, with an atony, usually of the ascending part of the colon. Such abnormalities of intestinal movements may just as well be consequences as causal factors of constipation. They may, however, be cooperating factors which aggravate constipation, just as a diet containing too little residue for stimulation of the peristalsis or an abnormal length or course of the colon. As a matter of fact, we are not taking into consideration here the small group of cases in which obvious anatomical abnormalities, such as Hirschsprung's disease or a functional slowing down of the peristalsis as in hypothyroidism, produce constipation. We cannot generally admit that the asthenic type of individual is particularly inclined to suffer from the atonic variety of constipation, whereas hypersthenic

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robust individuals more frequently exhibit its spastic variety (Soper) (2)).

The chief causal factor is, in our opinion, in the vast majority of cases the acquired torpor recti, that is, the loss of the specific sensation of the rectum which produces the desire to empty its contents. So it is ultimately what is called domestication, that is, the artificial adaptation of the organism to the requirements of civilization, which chiefly accounts for the frequency of habitual constipation. The correctness of this view is proved *ex juvantibus*, that is, by the effect of the treatment. It is generally admitted today that the main stress should be laid on the change of habits of constipated patients, but there is still much controversy as to whether or not mild laxatives, enemas, or a rough diet containing plenty of refuse should be prescribed in addition to the regulation of habits.

The experience of many years has taught me that it is not essential whether or not such additional prescriptions are given to the patient. What is prescribed is less important than by whom and how it is done. In other words, the psychological factor is of prime importance in success. This factor helps to establish the lost regularity of the defecation reflex act by creating anew a conditioned reflex and by training anew the sensitiveness of the rectum which had been lost. It must be emphasized that not any single point in the following prescription, but the total, is essential tending towards a systemic training of the reflex act and toward establishing a conditioned reflex. The details of the prescription given to constipated patients are as follows:

1. When you awake in the morning, uncover your abdomen for five minutes in order to expose your bowels to the cool air and to stimulate the intestinal movements.
2. Drink a glass of cold water with one tablespoonful of lactose dissolved in it.
3. Take some light physical exercise, and particularly contract and relax alternately your abdominal muscles twenty times in the upright position, which acts as a mild massage to the bowels.
4. Use the bathroom in any case 20 minutes after breakfast, but do not worry if you are not successful in emptying your bowels the first days. The bowels must be trained to act at this regular time just as you have to train a child or a dog to empty his bowels at a regular time.
5. Pay attention to this latter act from the moment of waking.
6. Do not take any purgatives. If necessary, take an enema with lukewarm water or a thin infusion of matricaria every third day as long as the spontaneous defecation act is still not possible.
7. Never suppress the desire to defecate in any circumstances.

This is the essential of the prescription used which proved to be successful in the vast majority of cases. Whether or not any additional dietary advice is given is unimportant from the point of view of the rationale of the treatment. It was used if a so-called intelligent patient believed in a diet and would have been disappointed without it. Only in exceptional cases was the

regulation of the diet necessitated by obvious nutritional indiscretions.

Spontaneous defecation may occur after one to ten days; it may, however, take longer, in order to establish the timed, conditioned reflex. After a period of about three weeks of satisfactory spontaneous bowel action the successive relief of the prescribed regimen may be tried. As a matter of fact, the patient must be fully informed about the necessity of keeping on the regular habit.

On account of the excellent results of this simple treatment it appears questionable how far a dietetic regimen acts directly by its physical and chemical constituents and how far a psychological factor accounts for the success. Alvarez (3) criticized, with good reason, the routine prescription of rough, indigestible food to some hypersensitive individuals whose intestines are easily upset by a heavy overload. The same doubt may arise if Borsook et al (4) had excellent results in the treatment of constipation with Vitamin B and if they conclude that partial Vitamin B-deficiency (or suboptimal intake) is probably one of the factors of the common constipation.

Many constipated persons suffer a great deal from what has been and is still frequently called enterogenic autointoxication. Those individuals feel "poisoned," miserable, are tired, bad tempered, and may have headache and no appetite. Although autointoxication by resorption of poisons from the intestines seems to be the most plausible explanation, such a thing has never been proved in constipated individuals.

Alvarez (3) and I (5), independent of each other, have emphasized that it is rather an upset of the central nervous system, produced mechanically by distention of the rectum in sensitive persons, than a resorption of intestinal chemical products which accounts for the distress of constipated persons. As a rule, the patients feel relieved immediately after a bowel movement. This can be explained only by the removal of a mechanical factor, not by the cure of a chemical poisoning.

I have ranked the malaise of constipated individuals with what the French school calls "cénestopathies," that is, an alteration of such general sensations as hunger, thirst, exhaustion, sexual libido, etc. In German psychology these general sensations are called "Gemeingefühle." To "feel fine" or to "feel badly" are statements concerning a certain group of this type of general sensations. The alteration of these sensations in constipated persons is apparently brought about by a reflex from the distended rectum. The more or less pleasant sensation of a just emptied ampulla in normal persons represents the contrast to the sensations of constipated individuals. This also points towards a reflex nervous mechanism and speaks against the theory of enterogenous autointoxication.

As far as the probability of such an autointoxication is concerned, Alvarez (3) points out that it is most likely to occur after purgation or in the presence of diarrhea but "that the individual is safest from auto-intoxication when constipated" (i.e. pag. 209). Some support to this view is given by the experiments of

my former coworkers in Vienna, Taubenhaus and Amann (6). They studied the water resorption from the emptied rectum in both normal and constipated individuals. Twenty cc. of a 1% solution of sodium fluorescein was injected into the empty rectum and the amount of sodium fluorescein excreted in the urine was determined every 30 minutes for three hours. The surprising result was a markedly lower resorption from the rectum of constipated than of normal individuals. When the constipation was cured and the patients had regular, spontaneous bowel movements, the resorption was found to be increased to the normal level. The rectal resorption of water or sodium fluorescein, respectively, of normal persons could not be altered by producing an artificial constipation with opium. It became diminished, however, by the administration of calcium carbonate per os. A satisfactory explanation of these unexpected findings has not been given. Yet it seems to me as if a depression of the sensitiveness of the rectum, which is supposed to exist in most of the cases of habitual constipation, were associated with a diminished resorptive function of the intestinal wall. The condition of the nervous system is apparently the common link between both phenomena, constipation and diminished resorption.

There is some evidence of quite a different implication of the nervous system in the act of resorption from the rectum. I showed, together with J. Monguió (7), that the rectal resorption of water, both cold and warm, even in so small quantities as 20 cc. is regularly followed by a decrease of blood sugar, of 20 mg. % on the average, in two to three hours. Inflation of the rectum with air or CO<sub>2</sub>, as well as an intensive cold stimulus by a piece of ice, failed to provoke the drop of blood sugar. A hypoglycemic action of extracts of the rectal mucosa could not be demonstrated by my co-worker, Monguió (8). It is therefore probable that the act of resorption itself elicits reflex effects upon distant organs. Garbat and Jacobi (9) found that the introduction of various solutions into the upper rectum, such as physiologic saline, indigo carmine, peptonized milk, methylene blue, dextrose and phenolphthalein, produces a drainage of the bile into the duodenum. They take into consideration either a direct

stimulation of the liver cells from the absorption of the instilled fluids into the portal system or a reflex nervous phenomenon. Inflation of the lower bowel with air failed to provoke a bile flow in their experiments. Hence it seems that these experiments, too, bespeak a reflex nervous phenomenon elicited by the act of resorption from the rectal mucosa. Further studies, however, are necessary to elucidate these interesting phenomena.

As I pointed out above, we have to consider a diminished sensitiveness of the rectum as the main causal factor of habitual constipation. Occasionally one meets with a psychoneurotic condition characterized by a hypersensitiveness of the rectal wall which induces an inadequate and not justified sensation of a filled ampulla. These patients feel constipated and may have the desire to empty their rectum every hour, as a matter of fact, without success. The rectum is empty but the misleading sensation of its being filled bothers those individuals a great deal. Those who are not familiar with this type of neurosis and do not take a thorough history may treat the patient for constipation or colitis in spite of negative physical findings. It is a dysaesthesia rather than a hyperaesthesia of the rectum which represents the essential disorder in this condition. Although such cases may be of particular interest to the psychoanalyst, it is important for the practitioner to be acquainted with them and to be able to make the correct diagnosis. The treatment has to be a psychological one, no matter which variety of psychotherapy be chosen.

"Psycho-somatic gastro-enterology" is the latest slogan to be met with in American literature (10). The word is new, but its meaning is as old as practical medicine. It was Plato who expressed his opinion as follows: "The greatest mistake in the treatment of disease is that there exist physicians taking care of the body and physicians taking care of the soul, as these ought not to be separated from each other . . . but just this fact is overlooked by the Greek physicians and therefore many diseases escape them, as they never see the whole." These words could have been written in our days and they certainly do not pertain to Greek physicians only.

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## Volvulus of the Stomach

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**V**OLVULUS of the stomach, in its acute form, is a serious but uncommon surgical emergency. The diagnosis is usually made at operation or at autopsy. Intermittent volvulus with less violent symptoms is less often recognized, and the opportunity for thorough clinical and roentgenologic study is infrequent. It was thought important, therefore, to discuss a case of intermittent volvulus of the stomach not only because of its special clinical interest as an unusual entity, but particularly because of some unusual features disclosed by the roentgenologic examination.

### CASE REPORT

Mrs. M. F. (M.G.H. No. 120666), a 23 year old housewife entered the hospital because of recurrent attacks of epigastric discomfort and pain during meals for 5 months. The pain almost always came on during a meal and had no radiation except occasionally into the left upper quadrant of the abdomen. The patient at times complained of epigastric discomfort during the night associated with gaseous eructations. The character of the food eaten had little influence on the character or severity of the symptoms except that liquids were apt to be more troublesome than solid food. She volunteered the information that frequently relief came when she "felt something drop in the stomach," (in the case of liquids, "with a splash").

Three and a half months and again three weeks before admission she had attacks of sudden severe cramplike epigastric pain while eating. The pain on each occasion was excruciating and made her feel faint, but she did not vomit. The attacks lasted about 2 hours and then gradually subsided. Since her second attack, however, she has had persistent dull pain in the left hypochondrium, in addition to the discomfort while eating. She had also noticed increasing constipation since the onset of the present illness.

A modified Sippy diet for suspected peptic ulcer had no effect other than to increase her malnutrition, which had already become noticeable since the intake of food had become associated with such unpleasant symptoms. The patient was finally told that she had a "bleeding ulcer" and operation was advised, but she came to the hospital for further study and treatment.

Physical examination revealed an undernourished asthenic young woman, about 15 pounds underweight and in no obvious distress at the time. The liver edge was palpable in the epigastrium but not otherwise abnormal. The remainder of the physical examination was entirely negative. Her blood pressure was 100 systolic and 60-70 diastolic. A gastric analysis showed no abnormality and there was neither gross nor occult blood in a stool specimen.

A roentgenologic examination was done to rule out organic disease within the gastro-intestinal tract, and adequate cause for her symptoms was disclosed. The

esophagus was normal in appearance. As the barium entered the stomach, however, its progress was obstructed in the mid portion of the descending part of the body of the stomach. After a delay of about 20 seconds, the opaque meal fell to the lower pole of the stomach, but a constant narrowing remained at the point of initial delay. In this area, the mucosal folds presented a definite twist (see Figs. 1 and 4a). On leaving the dependent portion of the stomach, the column of barium, instead of proceeding to



Fig. 1. Stomach during the volvulus, in supine position. Note twist of the folds (→). The distended air filled loop of the transverse colon passes across the upper half of the stomach (see haustral markings).

the right into the antrum, turned to the left and continued upward again, finally crossing to the right, anterior to the body of the stomach. The administration of more barium filled the stomach further, but its shape as well as the twist of its mucosal folds remained unchanged even after complete filling. The cardia, pylorus, and the duodenum were always in normal position. The transverse colon was outlined by a greater content of gas than normal. Instead of lying in its normal position below the

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greater curvature, it crossed the upper portion of the stomach at a high level (see Fig. 2).

Examination in the lateral view was of interest (see Fig. 5). The inferior pole of the stomach which normally lies anteriorly lay far posteriorly against the vertebral column. The transverse colon was displaced superiorly and lay anteriorly to the body of the stomach. The study was continued for one hour, and the peculiar relationships just described persisted in spite of changes in the position of the patient (prone, supine, and upright).

The roentgenologic examination was repeated two days later and the stomach appeared entirely normal in shape and position (see Fig. 3a). At this time, marked experimental distension of the colon with air moved the stomach upward but failed to reproduce the volvulus (see Fig. 3b). In the meantime, the patient volunteered that her symp-

The abnormal mobility was repaired by fixation of the anterior wall of the stomach to the parietal peritoneum by means of interrupted sutures. The patient experienced an uneventful convalescence, and roentgen examination of the gastro-intestinal tract 11 days after the operation showed the stomach lying close to the anterior abdominal wall and functioning normally.

The patient was seen again six months later. She was relieved of her symptoms and had gained ten pounds in weight. Re-examination of the gastro-intestinal tract showed normal position and function except that the colon was outlined by an abnormal amount of gas.

### COMMENT

Isolated cases of gastric volvulus have been reported since 1866 (Berti). Berg, in 1895, performed the first

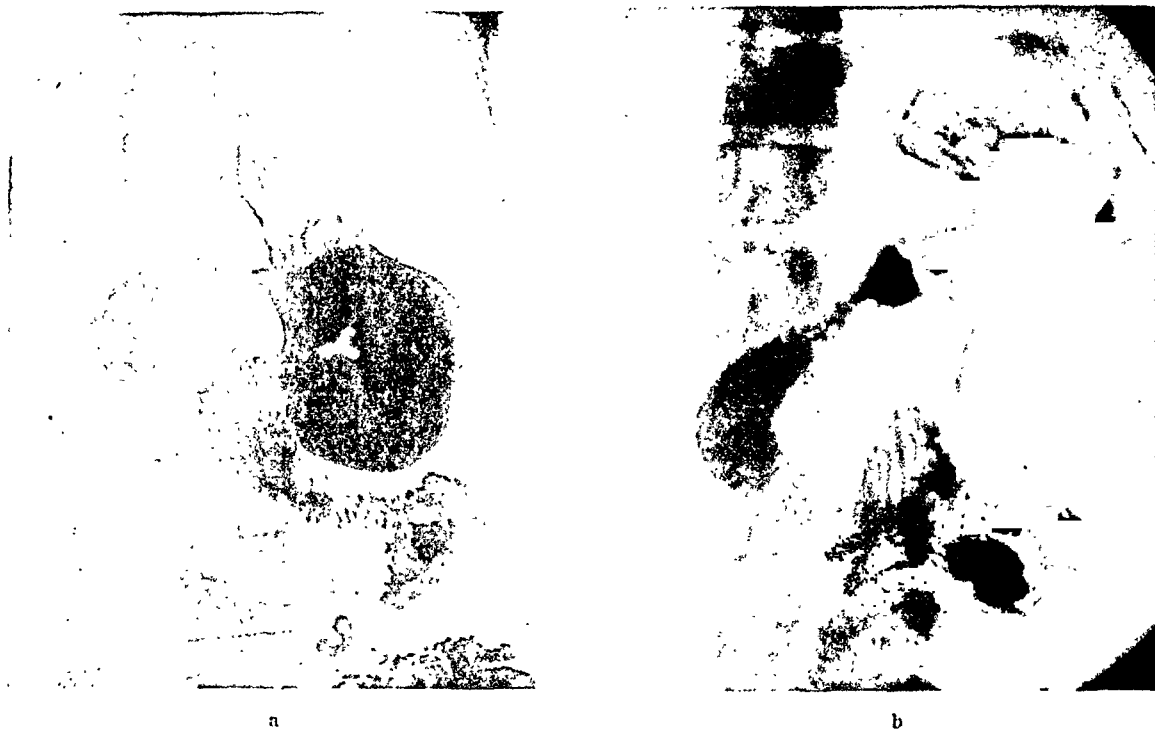


Fig. 2. Picture of volvulus in supine position. (a) Straight postero-anterior view. (b) Right anterior oblique view.

toms had improved somewhat but had not entirely disappeared.

The study summarized above disclosed three points of practical significance. 1. The presenting symptoms were probably due to volvulus of the stomach. 2. The volvulus was intermittent. 3. The production of volvulus was associated with, and possibly dependent upon, posterior displacement of the movable portion of the stomach. In fact, it seemed that if backward displacement of the stomach could be prevented, volvulus could not possibly take place. Accordingly, an anterior gastropexy was proposed for symptomatic relief and for removing the possibility of acute torsion of the stomach.

At operation the stomach was found to show extraordinary mobility. The volvulus could be reproduced by allowing the stomach to fall posteriorly into the left upper quadrant. During this maneuver, the transverse colon followed the stomach upward and lay across it anteriorly.

operation for its relief. A number of different types of volvulus have been described. The stomach may rotate around its longitudinal axis ("organo-axial volvulus"), or it may rotate around an axis at right angles to its length ("mesentero-axial volvulus"). The rotation may take place to the right or to the left; it may involve the whole stomach or only a part of it.

The symptomatology is readily explained by the roentgenologic findings as in the case reported above, or by the anatomic findings at operation. The cases described in the literature may be divided into two groups, those with severe, often dramatic symptoms and signs, and those with relatively mild but recurrent symptoms. The early cases reported in the literature belong mostly to the first group and many of them ended fatally, (cf. Borchardt, Peyer, Haberer, Kocher,

Buchanan, Morrison). In these acute cases, the twist produces early closure of the pylorus followed by distension of the stomach. The cardia closes shortly afterward and this increases the distension. The anatomical changes readily account for the presenting symptoms. There is epigastric pain, usually severe, soon followed by vomiting. The vomiting does not persist but is early replaced by uncontrollable retching. The upper abdomen rapidly becomes distended, and, in contrast with other forms of distension, it is im-

possible to pass a stomach tube by the cardia. At operation one finds a bluish cystic mass in the upper abdomen covered by gastrocolic omentum. The tumor resembles a stomach so little that it has been tapped as a cyst resulting in the withdrawal of gastric juice (Morrison). The mortality in this group has been high.

The cases described more recently belong to the group with less severe but recurrent symptoms (Rosselet, Weiss, Jean, Friedrich, Choicy and Babaianz,



Fig. 3. Pictures of the stomach after spontaneous reduction of the volvulus two days following the first examination. (a) Pa view. (b) Pa view after experimental insufflation of the colon with air. The stomach is displaced upwards but not twisted (arrow = duodenal cap).

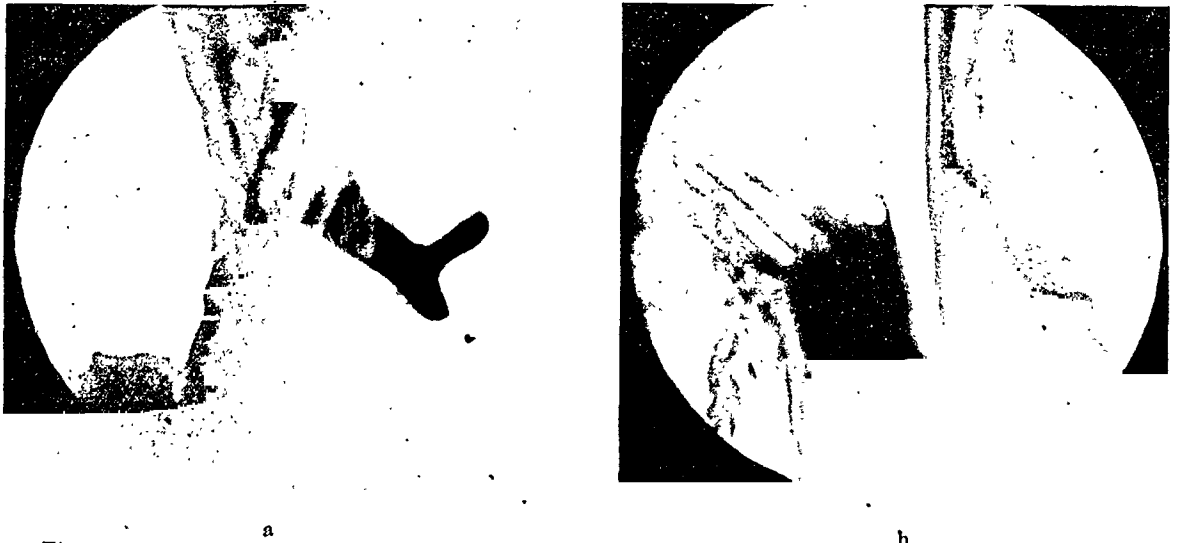


Fig. 4. "Spot films" of the mid portion of the body of the stomach. (a) During the time of the volvulus (see twist of the mucosal folds), antrum to the left of the body of the stomach. (b) The same area after reduction of the volvulus, the folds are untwisted, the antrum lies to the right of the body.

Aschner, Stepp and Kuhlmann, Singleton). The case histories often resemble those of patients with peptic ulcer, but, in contrast to these, patients with intermittent volvulus complain of distress and discomfort usually during a meal, as in the case described above, or directly after it.

The etiology or predisposing causes for volvulus of the stomach are not clear. Some instances have been reported in association with diaphragmatic hernia, hour-glass deformity of the stomach, gastric ulcer, and even with carcinoma of the stomach. Volvulus in these cases could be attributed to organic lesions described, but the group in which no organic lesion is found associated with the volvulus remains unexplained (cf. Buchanan). Over-distension of the stomach has been reported as a causative factor. In the case reported

twists are readily detected in the high-lying stomachs of obese individuals. These, however, should not be classed as true volvulus even if the displacement were so marked as to turn the greater curvature upward. To this group probably belong a large number of cases reported in the literature as true volvulus, particularly the type described as organoaxial in which there is anterior rotation of the lower part of the stomach to the right (see Fig. 6.). The "upside-down" appearance of the high stomach commonly found in eventration of the diaphragm is an example of the same phenomenon. Many of the cases reported as volvulus, but probably belonging to this false group, are described as showing no change in the position of the stomach with repeated examinations. Our own experience has been the same in cases of simple upward displacement of the stomach.

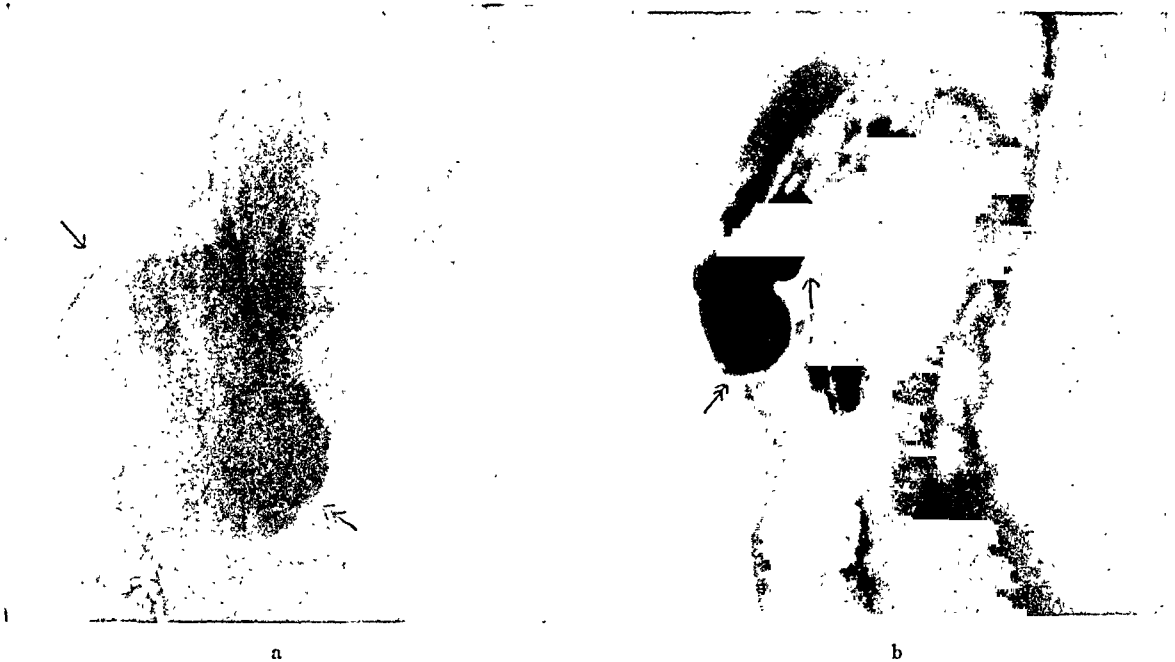


Fig. 5. Lateral views of the stomach. (a) During the time of the volvulus. Note the posterior displacement of the stomach, the stomach overlying the lumbar spine. Single arrow = duodenal cap; double arrow = lower pole of stomach. (b) After reduction. The stomach now lies far anteriorly close to the abdominal wall. Single arrow = duodenal cap; double arrow = lower pole of stomach.

here, however, the stomach was practically empty when the volvulus was discovered. Gaseous distension of the colon has been a common finding in the reported cases of volvulus of the stomach, a fact which has prompted several writers to consider it of causative importance. To test this idea, the colon in the case presented above was distended with air to the limit of safety. The volvulus could not be reproduced (Fig. 5b). The stomach was displaced upward, but did not become twisted. The distension observed in these cases, then, is not etiologic.

A distinction should be made between true volvulus and simple upward displacement of the stomach. The displacement of any organ which, like the stomach, is suspended from two more or less fixed points is necessarily accompanied by some rotation of the organ with twisting usually close to the fixed points. Such slight

The position of the stomach in these individuals is fairly well fixed.

The distinction between true volvulus and simple displacement of the stomach is not only of theoretical significance for diagnosis and classification, but also of practical importance for treatment. In contrast to the fixation of the stomach observed in simple displacement, making acute volvulus even less likely than in the normal, true volvulus usually occurs in asthenic ptotic individuals with unusually long and mobile mesenteries and ligaments. The danger of acute volvulus in such cases is appreciable.

There is little question concerning the treatment of acute volvulus of the stomach. Surgical reduction is the procedure of choice. The treatment for cases with less severe intermittent volvulus, however, is open to

discussion. The case presented above belongs to this group. Conservative treatment had been ineffective. The patient's symptoms persisted and she continued to lose weight on all of the diets she tried. Her stomach had an abnormal mobility and during volvulus showed an extraordinary posterior displacement. We could not discover a similar finding described in the literature, though it may have existed in other cases of true volvulus. This posterior displacement of the stomach

be prevented by anterior fixation of the stomach. In such cases, an anterior gastropexy is advisable not only to give symptomatic relief, but also to prevent the possibility of acute massive torsion at a later date.

### CONCLUSIONS

1. Volvulus of the stomach is a rare condition.
2. A case of partial volvulus of the stomach is reported.

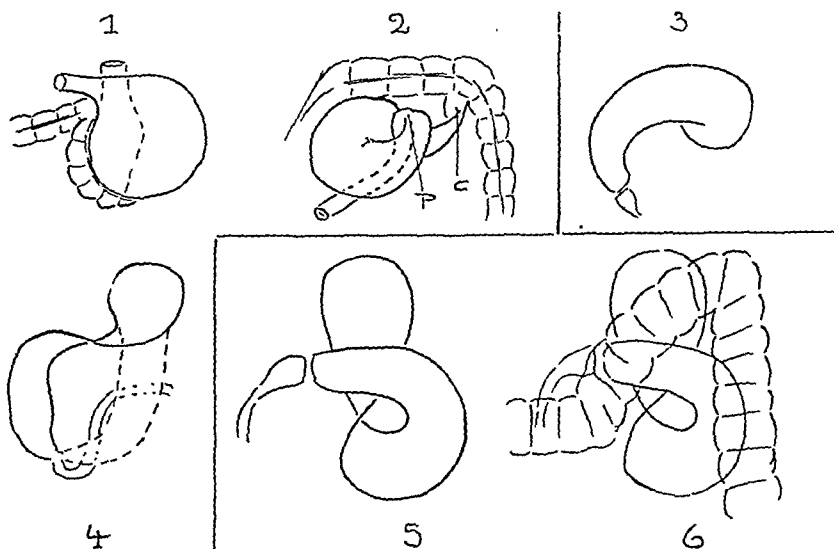


Fig. 6. Schematic sketch of (1) Buchanan's case. (2) Laewen's case. (3) High stomach, not infrequently but erroneously called volvulus. (4) Rosselet's case. (5 and 6) Authors' case.

is probably due to the fact that any true volvulus, because of its knotting effect, necessarily shortens the freely movable part of the stomach and brings it closer to the plane of its fixed points (cardia and pylorus), i.e. a plane closer to the spine. It seemed that posterior displacement of the stomach was part of the mechanism for the production of volvulus and that both could

3. The posterior displacement of the stomach during the volvulus is emphasized.

4. Unusual mobility of the stomach, found at operation, is thought to be of etiological significance in this case.

5. Gastropexy produced symptomatic relief in the case reported.

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## Editorials

### CENTRAL SEDATION AND DIGESTIVE DISORDERS

CLINICIANS have long felt that increased tone, motility, and secretory activity of the digestive tract are sometimes associated with central nervous system excitement. Evidence in support of this idea has been furnished in the now classic studies initiated

by Cushing. As a result, many physicians are accustomed to include central sedation in the therapy of digestive disorders. Unfortunately, such adjunctive therapy often becomes routinized and in this country frequently is limited to administration of the barbitals.

Choice of an appropriate central nervous system de-

pressant drug in any particular patient depends upon a variety of circumstances and upon detailed knowledge regarding the rates of absorption and elimination of the drug, the character of its action, and its potential accumulative toxicity. Routine repeated administration of any single sleep-producing drug is dangerous, because of the possibility of inducing cumulative poisoning. If a chronic condition is present, requiring repeated administration of a soporific agent, it is wise to vary the chemical type used in order to avoid cumulative toxicity from any one agent. Sodium bromide and the barbitals are slowly removed from the body, in many instances requiring at least several days for excretion to be complete. While some of the "shorter acting barbiturates," such as "Nembutal" (pentobarbital, NNR), "Cyclopal," "Seconal," and "Pentothal" are reputed to be rapidly eliminated from the body, the evidence is not fully convincing. On the other hand, ordinary doses of alcohol, chloral hydrate, and paraldehyde are detoxified within 12 hours. Sulphonal, carbromal and similar agents are more slowly removed from the body.

Under these circumstances it would seem wise to alternate various chemical types of soporific drugs, if more or less continued use is necessary in order to relieve the nervous strain and irritability of modern life which may be reflected in disturbances of the alimentary tract. It might be wise for example, to recommend two or three ounces of port wine one night, some paraldehyde the next, sodium bromide the third, barbitol the next, chloral hydrate the next, carbromal the next, and then return to port. With this procedure the possibility of cumulative poisoning with any one is very remote. While it might be objected that such a system is too complicated or expensive for the average patient, it might be retorted that just such attention to detail may be helpful to a nervous patient. In handling these conditions it is not ordinarily necessary to use a motor depressant, such as phenobarbital, or "Dilantin," nor does it seem justified to use the more expensive barbitol derivatives in preference to barbitol until their various claims of superiority are disinterestedly appraised.

It is important to estimate dosage carefully in accordance with the state of the individual. It is to be remembered that the level of central nervous system depression between "depression" and "anesthesia" is "delirium." If an individual is very tense and excited, an ordinary dose of a soporific drug may only reduce the level of central activity to "normal." It may require more than an ordinary dose in such a situation to bring the patient to a level of depression, sufficient to induce restful sleep. On the other hand if the individual is thoroughly exhausted, an ordinary dose may throw the patient into the stage of delirium. Dosage should also be adjusted to weight variations in relation to what is considered the "average" of 150 pounds. It is careful attention to details of this sort that may help to make drug therapy in digestive disorders even more successful than it now is.

Chauncey D. Leake, San Francisco.

#### THE VALUE OF GASTROSCOPY TODAY

IT may be permissible to add a few words to the excellent editorial written by Dr. Alvarez in Number 1, page 51, of this volume. After we have succeeded in demonstrating that behind the "indigestion" or

"nervous dyspepsia" severe organic diseases of the stomach are hidden, especially the various kinds of inflammation, it will be the outstanding task of our specialty to invent similarly reliable methods for the study of the small intestine. This seems to be a long way off, but in the meantime we should not forget that inflammation of the intestine often may be associated with inflammation of the stomach, and that the presence of mild inflammation in the stomach suggests the presence of similar inflammation in the small intestine.

Diarrhea is not a symptom of gastritis, but if in a case of diarrhea through studying the stools and looking into the sigmoid we can exclude disease of the colon, the gastroscopic finding of some gastritis speaks against mere psychoneurosis and should suggest the presence of a similar enteritis in the small bowel.

There is one point made by Dr. Alvarez on which I disagree. He inferred that physicians would object to having unnecessary gastroscopic examinations made on themselves or their relatives. In my practice I gastroscopize many parents of physicians. Usually a carcinoma of the stomach has been found and the physician wants to make sure first that it is present, and then he wants to get all the evidence he can as to its operability or inoperability. I gastroscopize also many wives of physicians and many physicians themselves. Many of these physicians are under the age of thirty-five. Often they are suffering from epigastric distress. Nothing was found on roentgenologic examination and the doctor wants to get a clear-cut diagnosis if he can. In many cases when some gastritis is found the doctor is glad to have me look at it through the gastroscope from time to time.

This attitude of physicians towards gastroscopy for themselves and mothers and wives is highly gratifying to me because it demonstrates what they really think of the procedure. Such an attitude will, I think, be found only where the procedure is recognized as being a minor one. To do gastroscopy only in an operating room will prevent its being used in daily routine. The introduction into the stomach of a flexible gastroscope is not much more disagreeable to the patient than is the introduction of a stomach tube, and much more valuable information can be secured with the gastroscope.

I agree with Dr. Alvarez that the evaluation of the symptoms of chronic gastritis is a difficult one, and I agree that even severe gastritis may be asymptomatic for considerable periods of time.

R. Schindler.

#### THE USE OF SECONAL AS A SEDATIVE PRIOR TO THE PASSING OF A DUODENAL TUBE

THE average diagnostic biliary drainage requires several hours, and all but the most phlegmatic patients become more or less restless before the procedure is completed. During the past two years, to help these persons, I have been giving a small quieting dose of Seconal (sodium propyl methyl carbinyl allyl barbiturate). This is a quick-acting hypnotic, the effect of which lasts only about six hours.

Forty patients, who were regarded as nervous, were each given three-fourths of a grain of Seconal before the attempt was made to pass the tube into the duodenum, and the results were satisfactory. There was

less restlessness and clock-watching, and I believe the method is worth following in the future.

Augustus A. Hall, Columbus, Ohio.

#### CHEWING AS AN AID TO RELAXATION

**T**HE thoughtful physician must often wonder what basic human need causes so many persons to chew gum violently and for long periods of time. There must be some reason for this behavior. Doubtless in many cases the swallowing of saliva tends to neutralize acid in the stomach. Also frequent swallowing, with the forcing downward of waves of contraction, must tend to keep reverse waves from running backward up the esophagus to produce belching, heartburn, and several types of discomfort. We know of persons with ulcer who sometimes, when they cannot leave their work to get some milk, can relieve hunger pain by chewing gum. As smokers know, the man who has been made very nervous by his efforts to give up the use of tobacco will often take refuge in gum chewing.

Recently H. L. Hollingworth published a monograph on the psychodynamics of chewing (*Arch. Psychol.*, July, 1939, page 90, also *Science*, October 27, 1939, page 385). Professor Hollingworth came to the conclusion that many motor automatisms are tension outlets. Other such automatisms are grimacing, fidgeting, wriggling, watch chain twiddling, coin-jingling, doodling, smoking, and in the case of women, knitting, crocheting and tatting.

In order to study the effect of chewing, a number of persons were watched without their knowledge throughout the working day and were rated from time to time on a scale of motor restlessness. A restless movement was regarded as any motor activity not useful in doing the work in hand. These persons were required at forty-five minute intervals to rate their subjective feelings of tension from extreme strain at one end of the scale to extreme relaxation at the other.

The workers all reported themselves as feeling more relaxed while chewing. On the whole, tension seemed thus to be reduced from 10 to 15 per cent. Measurements of muscular tension made from time to time indicated that during the periods of chewing it decreased about 5 per cent. Chewing while working did not interfere with the output, at least in several of the types of work studied. In number-checking and typing it improved the output—all of which will doubtless give much comfort to chewers and to the purveyors of gum and chewing tobacco.

W. C. A.

#### EFFECT OF SPINAL ANESTHESIA ON INTESTINAL ACTIVITY

**I**T has been known for some time that spinal anesthesia can increase intestinal activity, probably through removal of inhibitory impulses arriving by way of sympathetic nerves. At times the induction of spinal anesthesia will even bring relief in cases of dynamic or paralytic intestinal obstruction. Those who are interested in this phenomenon will find an introduction to the literature on the subject in an article by C. L. Burstein in the October, 1939, number of the *Proceedings of the Society for Experimental Biology and Medicine*, pages 291 to 293.

He reports studies done on six dogs with Thirry-Vella segments which showed that always, after the

induction of spinal anesthesia, there was a marked increase of the amplitude of the intestinal contractions. This effect persisted for thirty minutes after sensory and motor functions had returned in the animal's legs.

Unfortunately, the increase in tonus and peristaltic activity produced in this way can do harm as shown by the fact that in two cases of intestinal obstruction spinal anesthesia led to a rupture of a weakened segment of bowel.

Some reports have appeared recently of good results obtained in cases of megacolon and obstinate constipation with treatment by spinal anesthesia.

W. C. A.

#### A WAY IN WHICH CHRONIC LIFE-LONG DISEASE MIGHT BE PRODUCED

**I**N the November 17, 1939, issue of "Science" there is a note to the effect that Dr. E. L. Tatum has found that a certain bacterium can change the eye color of the little fruit flies which have been used so extensively in researches into the mechanisms underlying heredity. This is a remarkable discovery because such permanent changes in animals have hitherto been considered to be due only to a combination of those genes or tiny directors of heredity which, in large numbers, make up the several chromosomes in the nucleus.

The change from white to brown eyes was found to be brought about by a hormone produced by the bacterium, working in conjunction with tryptophane present in the food of the flies. The hormone produced by the bacterium appears to be identical with one which can be produced by the flies. Dr. Tatum made his discovery when the tryptophane used in feeding some flies became contaminated with the as yet unnamed bacterium.

One is led to wonder if some of those peculiar constitutionally inadequate persons who are born into families made up almost entirely of healthy people could have been injured in embryonic life by some such infection. It is to be hoped that the subject will receive much more study in the future.

W. C. A.

#### THE PROTECTION OF THE HEPATIC PARENCHYMA

**S**INCE the pioneer work of Opie and Alford, the effect of carbohydrates in protecting the liver against toxic substances has been abundantly confirmed by many investigators. It has, accordingly, become a well-established practice in the treatment of hepatic disease to administer a high carbohydrate diet, with little concern for other components of the food taken by the patient. Evidence accumulated in recent years indicates that there may be other factors of considerable importance. A high content of fat in the liver has long been known to predispose the organ to injury. In a general way, such an increased content of fat is believed to bear a reciprocal relation to that of glycogen. Ravdin, however, has shown that because of the slow mobilization of liver fat, the organ may have a relatively high content of fat and of glycogen at the same time. Under such circumstances, the hepatic cells are vulnerable to toxic substances in spite of their high content of glycogen.

Protein has long been interdicted as a component

of the diet of patients who have hepatic disease, and the physiologic studies on which this conclusion is based are well known. A high intake of meat proteins produces fatal intoxication of animals that have Eck fistulas; in dogs that have experimentally produced cirrhosis, meat or extracts of meat will induce ascites and edema. Vegetable or egg proteins have no such effect, so that it may be assumed that a qualitative difference exists between various proteins as far as their effects on the liver are concerned. There is, in fact, excellent experimental evidence to indicate that under certain conditions, protein may function as a protective substance in respect to induced hepatic injury.

Specific agents which are known to protect the liver against injury produced by carbon tetrachloride include the Japanese product, Yakitron (sometimes referred to as a "detoxicating hormone") xanthine and several of its various derivatives (Forbes and Neal). How these compounds exert their protective activity is not fully understood. Ravdin recently has pointed out that they may do so by virtue of the inflammatory reaction produced at the site of injection which of itself is capable of liberating protein-split products that are formed by increased protein catabolism. The protected livers of Ravdin's animals contained unusually large stores of glycogen, possibly formed from protein by a process of glucogenesis.

On the basis of the aforementioned experimental evidence it would seem logical to revise the usual diets now given to patients who have hepatic disease; a proper diet should include a liberal supply of protein from milk, eggs and vegetables, in addition to the increased content of carbohydrate. Fat should be moderately restricted, since over-feeding with it increases hepatic cellular deposits of fat and thus renders the cells vulnerable to toxic agents.

For bibliographic references and a more complete discourse on this interesting subject, the reader is referred to the article by Ravdin, Vars and Goldschmidt (1).

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A. M. Snell.

#### POSSIBLE ANIMAL CARRIERS FOR ORGANISMS AND VIRUSES PRODUCING DIARRHEA IN MAN

AS was shown by Richard Cabot many years ago and more recently by Philip Brown, in eight out of ten cases of diarrhea no organic disease can be found and no parasites can be demonstrated in the stools. In some of these cases the cause appears to be a nervous one, and in others the trouble may be due to sensitivity to one or more foods, but in others it would seem that some virus must be present. This is especially true in those few cases in which the patient eventually "peters out" and dies. In some of these cases we have seen the mesentery full of large lymph nodes which indicated strongly the presence of some infectious organism, yet none could be grown from tissue put through a Rosenow press.

Years ago a farmer's wife came to The Mayo Clinic complaining of a debilitating chronic diarrhea for which her home physicians could find neither cause

nor cure. After some of the clinicians had failed to throw any light on the nature of the disease, the patient asked to see Dr. Charles Mayo. After listening to the story, he turned, in his kindly and friendly way, to the husband and said, "What do *you* think is the cause of the diarrhea?" His answer was, "I think she caught it from the chickens. A lot of them have it, and she is always fussing with them." Dr. Mayo asked that some of the sick chickens be brought to the laboratory, and when they were examined they were found to be riddled with avian tuberculosis. When the woman's feces were examined, avian tubercle bacilli were recovered from them. One wonders if perhaps more persons with puzzling diarrhea may not have caught an infection from some domestic animal.

In the November, 1939, number of the "Proceedings of the Society for Experimental Biology and Medicine," Charles Bass has an article on the chronic ulcerative enteritis which often wipes out coveys of quail. This disease has been found to be due to a gram-negative spore-bearing anaerobic bacillus. Obviously if such a slowly growing, strictly anaerobic organism were the cause of diarrhea in some man or woman it would not be found during the routine culturing of the stools for dysentery bacilli.

Interestingly, in the quail this diarrhea-producing organism is transmitted through the egg to some of the chicks. It is conceivable, then, that organisms pathogenic for the intestine of man might be transmitted through the eggs of hens or ducks. Feldman has shown that such transmission of bacteria takes place in the case of avian tuberculosis. At any rate, those bacteriologists who are studying diarrheas in man may get some helpful ideas from this work of Dr. Bass.

W. C. A.

#### DIET AND CANCER

A GREAT deal has been published on diet and cancer without proving anything. The failure was due almost entirely to the fact that the work was done on man and not on animals, where conditions can be really controlled. Recently a little book was published by N. Waterman. The work was based on the study of animals developing tar cancer. As the writer points out, experiments dealing with transplanted tumors cannot give information about spontaneous tumor formation. When one is producing cancer by applying tar, the effect of diet can be determined both on the ease with which cancer can be started and also on the malignancy with which it goes on to kill the animal.

The results of Waterman's work as reported in a book review in the March number of the *Quarterly Review of Biology*, page 96, are as follows: 1. One must distinguish between the substances favoring the outbreak of carcinoma and those increasing malignancy. Applied to human conditions this means that prophylactic and therapeutic diets need not necessarily be the same. 2. A method is described which will express numerically the metastasis incidence in its relation to the degree of malignancy. 3. Among the classical foodstuffs (proteins, carbohydrates and fats) only the animal fats seem to have a frankly deleterious effect; the unfavorable influence of cholesterol seems to be due to the cholesterol esters. 4. As regards the

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MAY, 1940

vitamins, a comparison between the action of Vitamin A or the provitamin (carotene) in arachis oil and that of the same provitamin in olive oil shows that one has to be very careful in vitamin experiments, as the vehicle may be far from indifferent. Carotene in arachis oil seems to have a favorable effect and would especially appear to diminish the metastasis number. This was not the case when carotene was dissolved in olive oil.

The unfavorable effect of Vitamin B<sub>1</sub> as described in the case of inoculated tumors is certainly not present in tar cancer. Vitamin C appears to be distinctly favorable; therefore, these results are far from supporting the notion of a tumor-favoring action of tomato juice, which contains considerable quantities of Vitamin C.

W. C. A.

#### A COMPONENT OF BEEF INJURIOUS TO UREMIC RATS

IT has long been assumed by the medical profession that meat is injurious to all patients with nephritis. That this is not necessarily true was shown some years ago by Thomas Addis. He pointed out that in cases of severe nephritis or nephrosis it is essential to give considerable amounts of protein if only to replace the large amounts being lost in the urine. In such cases the giving of meat tends to cure the edema.

Many years ago in England a man wrote a book in which he summed up a large amount of research done in an effort to show which extractive of meat is toxic to the kidney. Actually, if we remember correctly, he didn't find any extractive that was decidedly toxic.

In a recent paper, Addis and Lew (J. Clin. Investigation, 18:773, 1939) reported studies made on rats first rendered anuric and uremic by the ligation of the vena cava above the entrance of the renal veins. These animals were fed several types of diet to see which foods would shorten life. Diets with a low protein content or with varying amounts of casein seemed to have no deleterious influence. The mortality rose when the diet contained large amounts of protein derived from dried liver, kidney and beef. An aqueous extract of beef produced a 52 per cent mortality, while an alcoholic extract had no bad effect. Finally, it was found that a solution of potassium acid phosphate and potassium chloride containing approximately the amounts of these substances as were in the watery meat extract had the same effect on the mortality rate of the rats as the meat extract did. The conclusion was then that the high potassium content of the meat diet was responsible for the high death rate of the animals fed this diet.

W. C. A.

#### THE ROENTGENOLOGIC APPEARANCE OF THE SEVERAL PARTS OF THE SMALL INTESTINE

IT is to be hoped that every gastro-enterologist read three papers by Chamberlin, Weber, and Kiefer in the October 21, 1939, number of the Journal of the A. M. A. There is great need today for more study of the small bowel and of its lesions. Chamberlin first described the appearance of the normal bowel and then its changed aspect in cases of several diseases. More descriptions of the roentgenologic appearance of the diseased small bowel were given by Weber. His ap-

pendent bibliography will be of help to all students of the subject. Kiefer's paper and the discussion that followed were also interesting and valuable.

W. C. A.

#### THE POSSIBLE VALUE OF TREATMENT WITH ADRENAL CORTICAL HORMONE IN CASES OF CHRONIC WEAKNESS AND FATIGUE

INTERNISTS are consulted by many patients whose principal complaint is that they feel weak and tired all the time. Especially when the blood pressure is found to be a little low and perhaps when the skin is somewhat pigmented, the question will arise: Can the syndrome be due to a mild Addison's disease in which the destruction of the adrenal glands is not complete? This question is going to come up for consideration even more frequently now that a synthetic corticosterone has become available.

The subject has been well discussed in a timely review by George W. Thorn in the May, 1939, number of the "American Journal of the Medical Sciences." More information is given by the same writer in an editorial in the "Annals of Internal Medicine" for September, 1939. Important is his conclusion that "It is possible that adrenal cortical hormone therapy may be of benefit in other disorders (not Addison's disease) but, to date, conclusive evidence has not been presented to substantiate this suggestion."

The experience of the men at The Mayo Clinic who have had the chance to study a few hundred cases of Addison's disease has left them with the impression that border-line conditions and "formes frustes" are rare. The factor of safety in the gland is so great that if even a few microscopic bits are left functioning the patient shows no sign suggesting Addison's disease. Furthermore, as pathologists know, at necropsies one rarely finds disease that has destroyed, let us say, one adrenal and half of the other. These glands are either not involved by tuberculosis or else they are totally destroyed by it.

Occasionally the pathologist will find some atrophy of the glands but then careful questioning of the family will fail to reveal any history of symptoms suggesting beginning Addison's disease. Sometimes, and this is the important point, the pathologist will find such marked destruction of the adrenals that he will wonder how the patient could have gone on living, and yet the history will show that before death came, perhaps from an accident, there were no symptoms to suggest the presence of such serious disease as was found.

A useful method of testing to see if a patient is on the verge of slipping into Addison's disease is to remove most of the sodium chloride from the diet. If the patient's adrenals are badly diseased this should throw him into a crisis with prostration and vomiting. It will not always do it, however, and there are rare cases of Addison's disease in which the test will not work. Another way of testing these patients is to measure the concentration of sodium and chloride in the urine under standard conditions, and another is to study the effect of adrenal cortical hormone on the renal excretion of sodium and potassium.

The experience of the men at The Mayo Clinic has led them to believe that it rarely pays to give cortical hormone to that commonly seen type of patient who is tired and weak. Gordon, Sevringhaus and Stark, how-



ever, reported that seventeen of thirty-two such patients were helped by the adrenal hormone; these patients were given also an extra amount of sodium chloride. It goes without saying that in such studies a great effort must be made to exclude the influence of enthusiasm and self-deception on the part of the patient and the physician. The literature is filled with descriptions of good therapeutic results which later could not be duplicated.

In normal men and women the repeated intravenous injection of cortical extract causes a decrease in renal excretion of sodium and chloride ions and an increased excretion of potassium. There is also a depression in the amount of oxygen consumed during exertion.

W. C. A.

#### THE HYPERSENSITIVENESS OF TISSUES THAT HAVE LOST THEIR AUTONOMIC NERVE CONTROL

WHEN smooth muscle in stomach or bowel cramps up, the ordinary observer might well assume that this muscle has received stimulation by way of nervous paths. *Actually, just the reverse may have happened.* A normal stream of inhibitory influences may well have been removed. For years it has been known that the sympathetic nerves to the stomach and bowel supply inhibitory influences, and extensive studies by Alvarez and Hosoi showed that the vagus nerves act in much the same way. Studies by Alvarez in which the reactions of the bowel to stimulation were observed for several minutes after the shutting off of the circulation to shorter or longer segments of small bowel showed that with the loss of circulation there appears a progressive loss of some inhibitory influence which seems to come by way of autonomic nerves interrupted by a synapse. Ordinarily this inhibitory influence keeps the whole bowel from responding instantly to some stimulus which shoots through the mesentery from one end of the digestive tract to the other. Normally, a stimulus anywhere in the bowel tends to produce a contraction which tends to move slowly caudad. When, however, the normal inhibitory influences are removed by section of the nerves, or by a period of anoxemia, or by the injection into the animal of a little nicotine, all parts of the bowel may respond to a stimulus almost instantly.

Interestingly, the system of nerves which produces this rapid long-distance conduction with a systolic type of response appears to have no synapses; it is highly resistant to anoxemia and to the influence of nicotine. Probably, unfortunately, the other system of nerves that normally keeps the bowel quiet and keeps it from responding violently and widely to every stimulus is easily injured by anoxemia or nicotine, and perhaps by other poisons.

There is still another way in which the intestine might easily be thrown into spasm and that is through the hypersensitization to hormones such as acetylcholine and epinephrine. This so-called law of denervation is well described by W. B. Cannon in the December, 1939, number of the American Journal of the Medical Sciences. This article should be read by all thoughtful physicians because it sums up years of careful work by Cannon and his associates and because the facts there presented can easily account for many of the trying symptoms of nervous patients.

As Cannon says, some fifty-five years ago Hughlings

Jackson pictured a hierarchy of functions in the central nervous system which probably developed during the course of vertebrate evolution. Jackson pointed out that a destructive lesion in the higher parts of the nervous system causes loss of control of lower parts, and with this loss of control there goes an increased activity and irritability in the lower levels. It seemed to him that many disturbances, such as the convulsions in epilepsy and in certain cases of brain tumor, could easily be explained along these lines.

Cannon and his students have now shown through years of experimentation that when the higher nervous control is taken off of a lower nervous station or off of muscle, that center or that muscle becomes sensitized and sometimes highly sensitized to some of those hormones which are now known to produce the same results as those seen after stimulation of nerves.

W. C. A.

#### EQUIVALENTS OF EPILEPSY

YEARS ago we called attention to the fact that probably the best explanation for many of the curious syndromes which puzzle the gastro-enterologist is that they are manifestations of the workings of the same nervous defect which in other members of the family produced insanity, epilepsy, dipsomania, deaf-mutism, feeble-mindedness, or extreme asthenia and constitutional inadequacy. We noted also that some of the relatives of epileptics show peculiar nervous disorders and problems of personality which seem to be due to the same irritability and explosiveness of temper which characterize their stricken relatives. Actually, some relatives of the epileptic seem to have all the symptoms except the fits.

Now come the workers with the encephalograph to show clearly that brain wave patterns characteristic of epilepsy can be found in at least one out of four of the parents and siblings of epileptics, even when these relatives never suffered with convulsive attacks or spells of unconsciousness (1). It has been found also at the University of Chicago that many of the problem children who go into spells of temper and unmanageableness have brain storms with the abnormal waves that are typical of epilepsy. Apparently in many cases the brain storm is there but for some reason it doesn't produce either unconsciousness or a convulsive seizure. Perhaps its potential is not great enough, or perhaps conditions in the brain are not such as to permit of such a seizure. Perhaps some defective gene is lacking, which, if added to the others present, would produce the fits.

At any rate, when a sullen looking, red faced patient comes in complaining of abdominal cramps, hunger pain, headache, and perhaps great irritability and irascibility, it is well to find out if any of the near relatives have had convulsive seizures or short attacks of unconsciousness or sullenness.

Some of these relatives of the epileptic give a history of being unable to eat with other persons. In a few that we have seen there were abnormalities in the sexual act such as precipitate ejaculation or a failure to ejaculate.

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W. C. A.

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*The Renal Digestive Reflex. J. Urol., 43:1, Jan., 1940.*

Smith and Orkin urged that patients who had had

Robert Turell.

Gastric Neurinoma. *Am. J. Roentgenology*, 43:61-65, Jan., 1940.

Maurice Feldman, Baltimore.

*The Effect of Peptic Ulcer in Cholecystography. Am. J. Roentgenology, 43:58-60, Jan., 1940.*

A study of 115 cases of peptic ulcer, on whom cholecystography was carried out, to determine the effect of peptic ulcer upon this test. The gall bladder shadow density was considered normal in 101 cases or 87.7 per cent. In 9 cases there was poor filling or faint shadows and in 5 non-filling was observed. Two of the latter 14 cases were accounted for as pathological, the remaining 12 cases of 10.4 per cent revealed an abnormal cholecystographic finding. There was no operative confirmation on the 12 cases. In these there was some question whether they represented cases of pathological gall bladders or cholecystographic changes resulting from high gastric acidities of peptic ulceration. Feldman believes that some cases of abnormal cholecys-

tographic findings may be due to peptic ulcer, but many are due to associated gall bladder pathology. This study corroborates the general belief that peptic ulcer is undoubtedly responsible, in probably a small percentage of cases, for non-filling of the gall bladder.

Maurice Feldman, Baltimore.

BARBER, A. H.

*Acute Torsion of the Gall Bladder. British Med. J., 2:1272-1273, Dec. 30, 1939.*

Torsion or axial rotation of the gall bladder cannot occur in a normally situated organ. In exceptional cases it is so elongated that the whole gall bladder lies below the anterior border of the liver; the fossa for the gall bladder is occupied by the lengthened cystic duct. In these circumstances the gall bladder is completely invested with peritoneum and hangs freely in the abdomen. The mechanism of producing the torsion would appear to be the movements of the gastro-intestinal tract.

Barber reports a case, which at operation the distended gall bladder popped out of the wound; it was about the size of an orange, abnormally situated and had twisted through 360 degrees in a clockwise direction. Its blood supply was cut off causing gangrene. The whole of the gall bladder was covered with peritoneum. The cystic duct was longer than usual, was imbedded in the fossa of the liver which normally is for the gall bladder. There were no stones.

Maurice Feldman, Baltimore.

PRATT, JOSEPH H.

*Acute Pancreatic Necrosis. The N. E. J. of Med., 222:47-53, 1940.*

Dr. Pratt who for many years has been a pioneer in the field of pancreatic disease summarizes his knowledge and experience in respect to pancreatic necrosis.

#### SYMPTOMS AND SIGNS

Most important is acute, agonizing, non-colicky but continuous pain, unrelieved by morphine. The pain is in the upper abdomen and its extension determines the amount of involvement of the pancreas. Necrosis of the head of the pancreas causes pain to the right of the midline.

Vomiting at times with hematemesis is a common symptom. The patient is very ill, cyanotic, and there is a scarcity of objective findings. The temperature and pulse may be normal at first. The epigastrium may be tender but muscle spasm is usually absent.

Given symptoms of gall bladder disease in an obese person who is suddenly seized with agonizing pain, unrelieved by morphine, with vomiting and collapse, the diagnosis of pancreatic necrosis must be considered.

The use of the diastase test is necessary to make the diagnosis.

#### PATHOLOGY

The disease is essentially an intoxication, not an infection. It can be simulated experimentally in dogs by occlusion of the pancreatic duct. In spite of the many theories involved as to how the disease arises clinically, none are satisfactory. The common-channel theory, the spasm of the sphincter of Oddi theory, and the theory of metaplasia of the duct epithelium with occlusion of one of the smaller ducts fail to satisfy all the criteria.

#### CLASSIFICATION OF CASES

##### Acute Pancreatic Edema

Often associated with gall stones and accompanies attacks of gall bladder disease. A high diastase value is diagnostic. When necrosis of the gland appears, the condition falls into the category of:

##### Acute Pancreatic Necrosis

In this group death may intervene in a few hours with the previously described symptomatology.

##### Suppurative Pancreatitis

In this group also belongs gangrene of the pancreas. Both conditions occur secondary to acute pancreatic necrosis if bacteria grow and lodge in the necrotic tissues. The syndrome appears after initial improvement in cases of acute pancreatic necrosis. Symptoms of sepsis with leukocytosis, extension of pain, and fever are prominent.

#### LABORATORY AIDS TO DIAGNOSIS

##### Increased Diastase Activity

When found in the urine and blood is most important. The method of Wohlgemuth is the most satisfactory and simple one. A fresh morning specimen of urine should be used. Blood serum can also be used. Tests must be performed early in the course of the disease in order to follow the diastase activity. A level of over 256 units in the urine must be had to be of diagnostic value. A positive test may not appear until after the first twenty-four hours in some cases.

##### Increased Lipase in the Blood

The method of Cherry and Crandall is quite satisfactory. Leukocytosis

Often exceeds 25,000. A rapid fall during the first week is a good prognostic sign.

##### Hyperglycemia

In 50 per cent of the cases, the blood sugar is elevated. A glucose-tolerance test even in the presence of normal levels is sometimes of value.

#### TREATMENT

Up to 1929 all surgical authorities agreed that early intervention was necessary. In that year Polya offered the first protest against this procedure. Since then there has been a definite tendency toward conservative treatment with a resultant lowering of the mortality rate by 50 per cent to as low as 7 per cent in some clinics. In cases of low-grade pancreatitis as well as in cases with severe hemorrhage, shock and toxemia, conservative treatment is the method of choice. However, where suppurative processes are present, drainage for the pus must be performed.

The view that the disease is an intoxication in which trypsin and split-protein products are absorbed by the lymphatics and blood vessels of the pancreas makes it obvious that incision or manipulation of the pancreas only further aggravates the condition.

##### HOLMGREN, I.

*Dyspepsia de Fermentation et Enterocolitis de Fermentation. Acta Med. Scand., 99(5):476-491, 6 figs., 1939.*

The dyspepsia due to fermentation is an intestinal infection accompanying anatomic changes in the colon; it is a colitis from fermentation. The patients have a deficiency of gastric hydrochloric acid and consequently enterocolitis from fermentation occurs in a greater proportion of achylie or hypoachylie (achlorhydric or hypochlorhydric) patients than in normal individuals. — J. F. Wilkinson (Courtesy of Biol. Abst.).

##### FARAH, ALFRED AND PINKSTON, J. O.

*Responses of Intestinal Smooth Muscle of the Dog to Benzedrine Sulphate (Phenyl-1, Amino-2 Propane Sulphate). J. of Phar. and Exper. Therap., 68:14, 1940.*

In forty-six experiments on isolated segments of the small intestine and colon from ten dogs the usual response to benzedrine sulfate in doses of from 0.3 to 150 gamma per cubic centimeter of bath fluid was a generalized relaxation (decrease of "tone") and a decrease in the amplitude of the pendular and peristaltic movements. The isolated segments from the colon were much more sensitive to benzedrine than were those from the small intestine. In experiments (balloon technique) on unanesthetized dogs

with Thiry-Vella fistulae of the ileum, benzedrine sulfate in doses of 0.25 to 5 mgm. per kilogram usually caused a generalized relaxation. Three dogs with fistulae of the colon were studied. In twenty experiments without anesthesia, benzedrine in doses of 0.1 to 2 mgm. per kilogram consistently caused marked inhibition of spontaneous movements. It is concluded that the colon is the most sensitive portion of the intestine to benzedrine and consistently shows a definite inhibition of spontaneous movements.

A. E. Meyer.

ANAGNOSTOPOULOS, CONSTANTIN

*Contribution à l'étude de la Pleuresie Droite Symptomatique de l'abcès Hépatique Amibien. (Contribution to the Study of the Right Sided Pleurisy Due to the Amebic Abscess of the Liver). La Presse Médicale, No. 1-2, p. 7, Jan., 1940.*

Right sided pleurisy is a serious complication of the amebic abscess of the liver. The diagnostic difficulty can sometimes be unsurmountable, and tuberculosis may be simulated. If there is an epidemic of amebic dysentery, or if the disease is endemic and amebas are found in the stools, the amebic etiology of the pleurisy may be suspected. Exploratory puncture of the liver and finding of characteristic tenderness of the intercostal interspaces will permit the diagnosis.

Rudolph Schindler.

NISHIMURA, MASAYA.

*Über die chemische Zusammensetzung der Gallensteine. J. Biochem. [Tokyo] 28(2):265-292, 21 figs., 1938.*

Gall stones of many kinds were examined with respect to their contents of cholesterol, fatty acid, lecithin, bile acid, bile pigment and inorganic substances. Stones containing Ca-salt of a fatty acid (3 cases) as the main component, are called "fatty acid chalkstones" (Fettsäurekalksteine). These stones have a special form. The content of bile acids is small in the stones and mainly composed of cholesterolin and fatty acids; it is greater in stones, containing a large amount of Ca and bile-pigment. There is usually more desoxycholic acid than cholic acid present. The fatty acid content is small in cholesterolin-rich stones, and large in bilirubin-chalkstones. The latter occur often in the Japanese. The fatty acid is mainly palmitic acid and appears only as the free acid, except in the cases of the fatty acid chalkstones. The lecithin content is usually very small. The chemical constitution of the nuclear parts and the shell differs somewhat. The bile acid content is always higher in the nuclear parts. In the stones removed by operation, no real pure cholesterolin-stones are to be found; they are, instead, more or less combination stones. The specific weight decreases in indirect proportion to the amount of the alcohol extract.—M. Neuhof (Courtesy of Biol. Abst.).

TAKEHARA, HIROYUKI.

*Untersuchungen über die Zusammensetzung der stickstoffhaltigen Bestandteile der Cäcumbüden des Kaninchens und des Hundes. J. Biochem. [Tokyo] 28(3): 463-472, 1938.*

Caecum of healthy and grown up dogs was used. The caecum material was separated into mucous membrane and muscles layer and kept under alcohol. The monoamino acids were obtained by hydrolysis with conc. H<sub>2</sub>SO<sub>4</sub> and followed esterification, distillation and saponification; the individual amino acids were separated as Cu-salts. Choline was isolated as its platinate from the alcohol extract. The analyses gave the following results: In the rabbit, glycerol

and alanine were found to a relatively great extent in the mucosa. Glutamic acid, tyrosine, arginine and lysine were present in mucosa and muscularis. In the dogs, histidine, valine and alanine were obtained from the mucosa, glutamic acid from the muscularis, and lysine, arginine, tyrosine and alanine from both layers. About twice as much choline was found in the caecum wall of the rabbit as was found in the caecum of the dog. Choline was also present in greater quantities in the rabbit appendix than in the dog appendix. Lysine, proline, alanine, leucine, valine and tyrosine were present in greater quantities in the caecum of the dog than in the caecum of the rabbit; with alanine the reverse was true.—M. Neuhof (Courtesy of Biol. Abst.).

MALTESON, C. AND WEIGHMANN, R.

*Über den Sekretionsablauf der Unterkieferdrüse bei Chordareizung. Pflügers Arch. ges. Physiol., 241(5/6): 641-650, 3 figs., 1939.*

In dogs in morphine-pernoctone or in chloralose narcosis a continuous secretion-tachogram of the submaxillary gland was recorded, and either the chorda tympani or the lingual nerve stimulated by alternating currents of a frequency from 10-1500/sec. or by repeated (2 to 4 per sec.) condenser discharges of an RC or 10-20/sec. Stimulation with a low frequency current or with the condenser discharges produces a secretion increasing soon to a maximum, which is sustained until the end of the stimulation, where after the secretion diminishes rapidly. Increase as well as decrease of this type of secretion follows an exponential curve. With high frequency stimulation a polyphasic secretion is obtained due to stimulation effects upon vasomotor fibers. Physostigmine does not change the threshold of the nerve-gland system but increases decidedly the effect of supra-threshold stimulations and lengthens distinctly the after-secretion following cessation of the stimuli.—E. Fischer (Courtesy of Biol. Abst.).

WEIR, JAMES F.

*Atrophy and Necrosis of the Liver Without Jaundice. Ann. Internat. Med., 12(11):1845-1854, 1939.*

Many cases of liver damage occur without jaundice but with ascites, pruritus, hematemesis, melanoderma, or enlargement of liver or spleen. The cholecystographic examination, the bromsulphalein test, and the van den Bergh reaction are the most valuable tests to perform. 4 types of cases are cited: atrophy associated with disease of the gall bladder and biliary tract; atrophy associated with syphilis or with its treatment; atrophy of exogenous toxic origin; atrophy unassociated with other diseases. Liver damage is suspected when the patient complains of recurring mild indigestion, anorexia, nausea, constipation, headaches, weakness and loss of weight.—M. L. Ilsley (Courtesy of Biol. Abst.).

KIHARA, YASUO.

*Desoxycholsäure aus Fuchsgalle (Vulpes). J. Biochem. [Tokyo] 27(3):363-366, 1938.*

The formation of bile acids can be influenced quantitatively by the food. At the present, however, it is uncertain if the desoxycholic acid in the bile of herbivorous animals is due to the plant components in their food. Experiments to test this question were done on silver foxes. The special food mixture of 500-6— g. per day consisted of: 50 g. animal, and 50 g. fish meat, ¼ of chicken egg, 100 g. cow's milk, rice-, wheat- and corn flour, carrots, potatoes, green vegetables and fruit. The bile of the silver foxes, fed with this mixture, contained, besides cholic acid, relatively great amounts of desoxycholic acid. The quantitative relation of both acids was about 1:5 (to 1:6).—M. Neuhof (Courtesy of Biol. Abst.).

## Book Reviews

**Headache and Head Pains.** By Walter F. Dutton. Philadelphia, F. A. Davis Company, 301 pp., 1939. Price \$4.50.

For those physicians who rejoice in a sort of encyclopedia in which they can find all the possible causes and types of a disease listed, together with all the forms of treatment that have ever been advocated and later forgotten, this book will be a delight. Here one finds articles on the headache of heartblock, of Addison's disease,

and of foreign bodies in the external meatus of the ear!

Those physicians who want a book which embodies wide clinical wisdom and good judgment will, we fear, be disappointed. This is the sort of book that could have been written about as well by the office nurse as by the physician. For instance, one has only to begin reading at page 245 to see that no effort has been made to discriminate between treatments. For Addison's disease, twenty-two remedies are advised, including cresote, glycerophosphates, strychnine, tuberculin and even metrazol. Anyone who has ever had much to do with Addison's disease

will wonder how long a patient would last after being shaken up with metrazol. For the headache of cerebral disease one finds the good old-fashioned advice to put a blister on the nape of the neck. On page 255 one finds twenty-nine treatments for diphtheria, including the Schick test and diet!

Obviously the writer of this book believes in accepting everything that has ever been suggested in the way of therapy. If he had any preferences in regard to treatments, he did not feel the need for expressing them. Unfortunately so much space was wasted on irrelevant material that when he came to the discussion of so important a condition as migraine, the author gave a most inadequate discussion. He apparently has heard of ergotamine tartrate, but he recommends the use of 8 minims! Apparently he doesn't know that it is a solid substance.

On page 57 one finds the treatment for chlorosis discussed. Apparently Dr. Dutton has not noticed that this disease went out of fashion some fifty or sixty years ago; so much so that no one is sure today what it was like. We are reminded of the annoyance of the teacher of Latin who one day wrote on the margin of a boy's Latin composition, "Will you kindly tell your grandfather that we don't use the ablative absolute so much today. That went out of fashion at Oxford in 1870."

**Recipes and Menus for Allergies.** By Myra May Haas, with a preface by Dr. Nathan Schaffer. New York, Dodd, Mead & Company, 250 pp., 1939. Price \$2.50.

Every unfortunate mother who has to cook for some asthmatic child who cannot touch eggs, milk or wheat will be glad to get hold of this book. Apparently Mrs. Haas was up against the problem herself, and while she was organizing information for her own needs, she thought she might as well pass it on to others. The result is a book of interesting looking recipes. Most appreciated by many people will be the recipes for the making of bread without egg, milk or wheat.

In his preface Dr. Schaffer supplies much valuable information to show the patient who is unable to handle some substance comfortably where he is likely to run into it.

**The Rectum and Colon.** By E. Parker Hayden. Philadelphia, Lea & Febiger, 434 pp., 1939. Price \$5.50.

Dr. Hayden has produced a very attractive book, well written, beautifully illustrated and beautifully printed. The material appears to have been well chosen, and Dr. Hayden evi-

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with functional indigestion and find that magnesium trisilicate "appears to be an efficient, non-toxic antacid, causes rapid disappearance of symptoms, promotes healing, rarely disturbs the motility of the gastro-intestinal tract, and produces no general side reactions."

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<sup>1</sup> Mutch, N., *Brit. M. J.* 1:143, 205, 254, 1936.  
<sup>2</sup> Tidmarsh, C. J., and Baxter, R. G., *Canad. M. A. J.* 39:338, Oct. 1938.

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## Contributions Made in 1939 to Knowledge in Regard to the Pancreas\*

By

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AMONG the increasing literature on the pancreas perhaps the greatest interest in 1939 was centered on the so-called lipotropic factor. Acute pancreatitis, especially of the transient (interstitial) type, continued to form a frequent topic. In addition there was a renewed attention in pancreatic function tests. Finally, a number of papers have appeared on carcinoma of the pancreas, reflecting, perhaps, the recent encouraging prospects of surgical excision. Only a portion of the large number of papers are reviewed herein; as a rule, single case reports and general reviews containing no new observations have not been mentioned. An attempt has been made to select only those the present author has considered significant particularly from the clinical point of view. As in the review (18) for 1938, disease of the islet tissue has been excluded.

*Carcinoma of the Pancreas.* Autopsy reports are contained in papers by Grauer (21), Duff (17), and D'Aunoy, Ogden and Alpert (11). There was, as usual, general agreement as to the rapidity with which the disease progresses, averaging less than a year from the onset of symptoms to a fatal outcome. Loss of weight and abdominal pain are mentioned as the most prominent clinical manifestations especially when the tumor is in the body and tail, i.e., when there is no jaundice. Duff reviewed 16 such cases and stated that spread is more rapid than when the tumor is in the head. The predominance of males over females is again emphasized, the relation being 7 to 1 in the report by D'Aunoy, Ogden and Alpert.

Because jaundice remains as the most definite diagnostic sign in a large proportion of patients with carcinoma of the head of the pancreas, early operation in jaundiced patients offers an obvious hope of cure. The case reported by Illingworth (25) is of special interest in this connection because the patient was operated on after only four weeks of jaundice. A tumor was found, a cholecystogastrostomy and gastroenterostomy carried out, followed eight weeks later (a wound infection was responsible for the delay) by a resection of the duodenum and pancreas including the tumor. The postoperative course was smooth and uneventful until seven weeks afterward when the patient, following a dietary indiscretion, developed acute abdominal symptoms and died. At autopsy a bile peritonitis was found. The cause was due to a technical error, i.e., a leak had occurred about the ligature at the end of the resected common duct. Doubtless, in subsequent cases, this pitfall will be avoided. Another case of carcinoma of the pancreas, successfully removed, was reported by Brunschwig and Childs (3). In this case, however, the tumor was really a carcinoid which was shelled out by opening the duodenum, the

bile and pancreatic ducts being reimplanted *in situ*. The symptoms presented by the patient, a 41 year old male, were increasing weakness and steatorrhea; the X-ray revealed a filling defect of the duodenum. The possibility of reimplantation of the pancreatic duct in the gastro-intestinal tract has usually been disregarded by most surgeons describing excision of pancreatic carcinoma. The experience of Harries (24) should therefore be mentioned. He cut across the main pancreatic duct during the course of a gastric resection for ulcer, but was able to successfully reimplant the duct by working through the opened duodenum. A similar operation has been described experimentally by Person and Glenn (33). Using the method of Tripodi and Sherwin they implanted the pancreatic duct into the stomach and were successful in 24 dogs. Of special additional interest is the fact that these workers found normal liver lipids (3 to 6%) in these experiments in contrast to five dogs in which the pancreatic ducts were ligated and the pancreas partially removed and which showed a high liver lipid content (8 to 18%). This last observation is of interest in considering the lipotropic factor (see below).

The practical possibility of cure in carcinoma of the head of the pancreas by excision often resolves itself into the frequent and difficult question of whether or not to operate early in a patient with jaundice of unexplained origin. If the patient has carcinoma of the head of the pancreas he should have the benefit of an early resection because of the rapid course of the disease; delay is fatal. On the other hand, if the jaundice is due to hepatitis or some other transient disease, delay is followed by improvement and a therapeutically useless operation is avoided. Recent studies of pancreatic function tests (as discussed below) should perhaps be used more often in helping to solve this problem. It may be that with the elimination of much of the danger of laparotomy in jaundice through the increasing use of Vitamin K there will be a tendency toward more frequent performance of operation in doubtful cases early rather than late in the course of the disease.

When the tumor is in the body of the pancreas the indication for operation is less definite but even more urgent; otherwise, these patients inevitably fall in the group of hopeless diseases. At present the only possibility of diagnosis and resection lies in carrying out exploratory laparotomy perhaps more often than is customary. Certainly, the point should be emphasized that a patient in the cancer age with severe unexplained epigastric pain and rapid loss of weight should be suspected of harboring a carcinoma of the body of the pancreas. Moersch and Comfort (30) have observed in two patients with carcinoma of the body of the pancreas a definite bulging of the gastric mucosa during gastroscopy, a procedure which may

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prove to be of special diagnostic value in these patients.

**Pancreatic Function Tests.** Study of duodenal contents as a means of measuring pancreatic function has enjoyed a renaissance in 1939. The largest series were reported by Comfort, Parker and Osterberg (8) who described findings in 111 patients, 17 of them normal adults. This is a valuable paper with extensive data accurately evaluated, and limitations clearly stated. They concluded that persistent absence of pancreatic enzymes (or very low concentration thereof) may be significant but only when more than one sample revealed the same finding. Such observations, however, were made only in 7 patients all of whom had steatorrhea. Although the pancreas was not observed anatomically in these cases, 5 had X-ray evidence of pancreatic calculi, one a pancreatic cyst, the other was a diabetic. In 6 other patients with steatorrhea (due to non-tropical sprue) the concentration of pancreatic enzymes was normal. Berger and Schnetz (1) found low ferment concentrations in the duodenal contents of 7 patients in all of whom the pancreatic lesions were confirmed by biopsy or autopsy material. Sugar tolerance curves were also obtained. There were 2 cases of lipomatosis of the pancreas, 2 of pancreatic necrosis, 2 of pancreatic edema and 1 of carcinoma.

Study of duodenal contents following the intravenous injection of a new secretin preparation as a stimulant of pancreatic secretion has been reported. Lagerlöf (26) is free of histamine and cholecystokinin. A double barrelled tube is used by this worker in order to separate gastric and duodenal secretions. During one hour after the injection of the secretin about 150 cc. of duodenal contents were obtained the volume apparently being in direct proportion to the dose of secretin injected. The presence of bile is said to indicate either an absence of or an abnormally functioning gall bladder; when normal, the gall bladder apparently absorbs all the hepatic bile which does not, therefore, appear in the duodenum. The data presented comprised tests on numerous normal adults as well as on 35 patients with pancreatitis, pancreatic stones and carcinoma of the pancreas. Of the 35 patients, the diagnosis was verified anatomically by operation or post-mortem in over half or 19 cases.

This secretin test has been tried in France by Chiray and Bolgert (6) and others and in this country by Diamond, Siegel, Gall and Karlen (12). The latter observers reported their findings on 22 adults, 14 of them normal. The 8 patients all showed deviations from the normal in at least one of the several factors measured, i.e., volume, bicarbonate content or ferment concentrations. In only one case, however, was the pancreas examined anatomically (autopsy); a carcinoma of the stomach and liver was found, the pancreas being small with no obstruction in the ducts.

**Pancreatic Insufficiency.** Experimental pancreatic insufficiency is discussed below in relation to fat metabolism and the lipotropic factor. As a clinical designation (18) this term is usually used in patients suffering from so-called pancreatogenous diarrhea, i.e., bulky stools containing unabsorbed fat (steatorrhea) and protein (creatorrhea). However, most observers agree that steatorrhea and creatorrhea are not always pancreatogenous and are to be distinguished in adults from sprue and in children from coeliac disease be-

cause in both of these conditions the pancreas is normal. Of interest in this connection is the case described by Lagerlöf (26) of a 29 year old male with steatorrhea since early childhood who revealed a normal secretory response to secretin, thus excluding pancreatic disease and establishing a diagnosis of intestinal infantilism (coeliac disease, non-tropical sprue). This patient also exhibited a flat sugar tolerance curve. Two fatal cases of congenital steatorrhea are described by Rauch, Litvak and Steiner (35) who emphasize, as did previous observers, the association of pulmonary symptoms with this disease; they also observed transitory glycosuria. In the one patient coming to autopsy fibromatosis of the pancreas was found as well as a fatty liver. A remarkable case of persistent steatorrhea in a 51 year old patient with relapsing allergic manifestations was described by Markel (27). De-insulinized pancreatic extract by mouth was followed by complete relief of symptoms which recurred on withdrawal of the pancreatic preparation. Another case of steatorrhea was described by Dubois-Ferrière (16). The patient was a 47 year old female with bulky stools of 1½ years duration. Undigested meat and a high percentage of neutral fats were noted in the stool. Duodenal contents following injection of secretin showed a diminished volume and a lipase content 1/10 of the normal. She also showed a flat oral sugar tolerance curve but a normal curve when the glucose was injected intravenously; the author inferred, therefore, that there was a disturbance in intestinal absorption but not in utilization of sugar. At autopsy the pancreas was large and the acini completely replaced by fat; the liver was small and cirrhotic with fatty infiltration. Cole (7) observed a patient with a fatty liver who at autopsy also showed an almost complete destruction of the pancreas as a result of repeated attacks of acute pancreatitis.

The use of raw (or dried) pancreas in 12 children with low blood lipids was described by Stoesser (37). These children were all suffering from a variety of severe infections which, according to this author, seemed to be associated with a fall in the serum lipids. As a result of this treatment all showed an increase in the serum lipids which was most striking in the cholesterol ester and phospholipid fractions. In view of the relationship of experimental pancreatic insufficiency with low serum lipids as discussed below these observations might indicate that pancreatic insufficiency may occur during severe infections in children.

These clinical observations have an obvious bearing on the relation of the pancreas to fat deposition in the liver and to blood lipids, particularly as it concerns the existence of a lipotropic pancreatic hormone. This relationship is now discussed in detail particularly on the basis of experimental studies about which there is still considerable difference of opinion.

**Pancreas and Fat Metabolism.** In last year's review (18) considerable experimental work was concerned with the existence of a lipotropic hormone in the pancreas, not present in pancreatic juice and not due to choline or protein. That such a hormone (lipocaic) is an internal secretion of the pancreas depends, as clearly expressed by its discoverer, Dragstedt (13), "on the recognition that the depancreatized dog fed on a mixed diet of protein, carbohydrate and fat is not restored to a normal state by the adequate adminis-



tration of insulin and pancreatic juice, and that the remaining deficiency is corrected by oral administration of pancreas or of certain extracts of pancreas but not of other organs." Dragstedt and his co-workers go on to say that at least 3 grams of betaine hydrochloride or 2 grams of choline daily was found effective in relieving the fatty liver in depancreatized dogs whereas 1 gm. of lipocaic containing but a few mg. of choline was effective. One gm. of choline plus a diet containing 38% casein was ineffective.

In favor of an internal lipotropic hormone were the observations that ligation of pancreatic ducts did not lead to fatty livers; complete excision of the pancreas was apparently necessary. Further experiments in 1939 have not confirmed these findings. The data presented by Person and Glenn have been mentioned already. A large series of such experiments has also been described by Montgomery, Entenman and Chaikoff (31). Careful ligation of the pancreatic ducts and separation of the head of the pancreas from the duodenum were carried out in 20 dogs; they were all given a mixed high vitamin diet. Nine of the dogs in 12 to 23 weeks lost considerable weight and developed livers with a high fat content (11 to 35%). Four dogs received insulin, lost less weight but in 16 to 20 weeks also had fatty livers (containing 6 to 34% fat). Six dogs were given raw pancreas, lost no weight and exhibited normal livers (fat content 1.8 to 3.4%). These observations, as suggested by the authors, certainly mean that unless ligation destroys an internal secretion either pancreatic juice or raw pancreas contains something which is necessary in promoting absorption of some dietary constituent which is the lipotropic factor.

Serum lipids have also been measured in studying the effect of the lipotropic factor. Thus Montgomery, Entenman and Chaikoff (32) described 4 dogs, completely depancreatized and maintained with insulin who developed low serum lipids following operation. On feeding pancreatic juice all showed a pronounced elevation after 20 days, which returned to the low level on withdrawal of the pancreatic juice in another 25 days. This observation would seem to show that pancreatic juice contains either the lipotropic factor or something which enables the body to absorb it from the food. These studies are to be contrasted with those reported by Dragstedt and his co-workers (14) who also studied depancreatized dogs fed a full diet and given insulin; a low serum lipid level was noted in 5 to 6 weeks, the fall being coincident with fatty infiltration of the liver. They found that lipocaic corrected the hypolipemia within a week. It should be pointed out, however, that pancreatic juice was apparently not given to these dogs. This may perhaps have some significance particularly in view of the criteria expressed by Dragstedt (quoted above). A full and excellent review of the literature on lipocaic is contained in papers by Dragstedt and his co-workers two of which have been already cited (13, 14, 15).

*Acute Pancreatitis.* There is a continued concern as to the advisability of conservative as opposed to operative therapy in acute pancreatitis. Although the trend has been away from immediate operation, there is a growing realization that acute pancreatitis is a generic term which includes two different diseases, one of which is the classic acute hemorrhagic or gangrenous

pancreatitis, often called acute pancreatic necrosis, the other a transient, less serious acute non-hemorrhagic, or interstitial pancreatitis, often called acute pancreatic edema. A striking summary of 10 cases, 5 of each type, has been reported by Casberg (5). All were treated without operation; the 5 in the first group all died, the 5 in the second group all recovered. Casberg discussed the diagnostic differences in the two groups noting among other things that all of the patients with acute interstitial pancreatitis entered the hospital with a past history of several similar attacks whereas in those with pancreatic necrosis no such history was obtained. This fact is evidence against the supposition that acute interstitial pancreatitis is merely a mild degree of or an early stage in the development of acute necrosis. The same inference is made by Meyer-May (28) who, in three years of service in French Indo-China, observed 27 cases of acute non-hemorrhagic pancreatitis but none of acute necrosis. This author described his experiences rather fully and was able to study the lesion microscopically in biopsies removed from the 9 patients in whom laparotomy was performed. This author used the term "attenuated" pancreatitis as well as edematous pancreatitis. He made no observations on the amylase content of blood or urine but did note a fall in the ferment content of duodenal contents in many patients. Many also had hyperglycemia. Because of the latter finding he gave these patients insulin and observed positive therapeutic effects in that the severity of the attacks was relieved.

A characteristic case of recurrent attacks of acute interstitial pancreatitis forms the subject of one of several English papers on acute pancreatitis by Cullinan and Stewart (10). The patient had had a cholecystectomy; the gall bladder contained three small stones and the pancreas was hard and indurated. Urinary amylase showed a high peak during each attack. Various drugs were tried with no effect; morphia was also of no value, but the attacks eventually grew less severe and finally ceased altogether.

Griessmann (22) described 80 cases of acute pancreatitis he observed in six years at the German clinic of Giessen; 30 of the patients had acute edema, 50 acute necrosis of the pancreas. There was no mortality in the former group whether operated on early or later (for associated biliary disease). In the group showing acute necrosis immediate operation was followed by a mortality of 34% whereas with delayed operation (average of 11 days after admission) the mortality fell to 13%. Of the whole series, 94% had biliary lesions though only 20% had stones. Biliary diversion was carried out in all cases at operation. He observed a diabetic sugar tolerance curve especially in the patients with acute necrosis. Mizuta and Tsuji (38) describe the medical and surgical aspects respectively of 243 cases of acute pancreatitis observed in Japan 1901-35. Of these 79 were falsely diagnosed as intestinal obstruction, acute appendicitis, or perforated peptic ulcer. Of 56 cases operated on 48 showed a hemorrhagic lesion; the mortality was 18%. Of 18 cases not operated on the 6 severe cases all died, 9 mild cases all recovered; this compares significantly with the series described by Casberg (5) as already mentioned. The Japanese authors make no mention of amylase studies but emphasize the severe excruciating character of the epigastric pain.



**Blood Amylase.** Observations of high blood amylase in acute pancreatitis are less numerous in 1939 than in last year's review. The paper of Casberg mentioned above contains graphs showing the rapid fall of high values in acute interstitial pancreatitis with the subsidence of the attack. Probst, Wheeler and Gray (34) studied patients with peptic ulcers perforating into the pancreas and have noted an elevation which as a rule was not as high as in acute pancreatitis. High urinary diastase values were observed by Smyth (36) in experimentally produced pancreatitis. Cope and his co-workers (9) report an elevation of blood amylase following experimental hypophysectomy. The magnitude of the rise was slight in comparison with the rise produced by pancreatic obstruction. Golden, Sieracki and Handelsman (20), for example, found increases as high as 250 times the normal in 48 hours after complete ligation of the pancreatic ducts in dogs. Unlike previous workers they found that in 3 of 4 dogs a high level persisted long after the pancreas had atrophied (many months).

**Pancreatic and Biliary Disease.** Most authors describing cases of pancreatitis usually report the frequency of associated biliary, especially cholecystic disease; the figures vary widely. Those reported by Griessmann have already been mentioned. Carter and Hotz (4) found among 53 patients with acute and chronic pancreatitis that only 6 did not have biliary disease. Their mortality was 8% in chronic pancreatitis and 53% in the acute group; drainage of the gall bladder or common duct was done in all. Wolfer (39) discussed again the theory that cholecystic disease may be caused by reflux of pancreatic juice into the biliary tract and presented a cholangiogram with a visualized pancreatic duct. This anatomical relationship between the pancreas and common duct was discussed at some length in last year's review (18).

Though many observers now believe that such a mixture of bile and pancreatic juice may by reflux lead to pancreatitis, a contrasting view is that of Bottin (2) who anastomosed the bile and pancreatic ducts in dogs and found no evidence of pancreatitis. He believes reflux of duodenal contents rather than bile is responsible for acute pancreatitis. It should be stated, however, that many of the older observations have shown that bile of various animals behave differently when they enter the pancreas. The bile of the cat, for example, provokes a severe edema if allowed to flow into the pancreas. In the goat it is apparently innocuous. In the mouse and rabbit, on the other hand, bile is apparently irritating. In the human the data is obviously indirect and may be interpreted in more than one way.

**Pancreatic Stones.** An extensive series of 65 operated and 139 non-operated cases of pancreatic lithiasis has been reviewed by Haggard and Kirtley (23). The one case described in detail was operated on and the stones extracted. There followed a pancreatic fistula which eventually healed after five months. While pancreatic juice was flowing they found that ephedrine produced a slight but definite decrease in secretion. These authors discussed the differential diagnosis emphasizing the tenderness over the pancreas, steatorrhea, glycosuria and especially the findings by X-ray aided by a tube in the duodenum. Gillies (19) described a young girl, age 15, with a history of abdominal pain since childhood and positive X-ray shadows. At operation the stones were removed and a T-tube inserted. A stricture developed following removal of the tube which required a second operation and reinsertion of a second T-tube which was later removed with permanent cure.

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## Calcification of the Pancreas\*

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**A**PPROXIMATELY one hundred and forty cases of pancreatic lithiasis have been reported in the literature since the first description by de Graaf, in 1664. Of these, twelve exhibited disseminated calcification of the gland. The first example of this type of calcification was reported by Allen (1) in 1903. A brief resume of these cases and a detailed report of the author's case constitute this paper.

### CASE REPORTS

Case 1. Allen (1), in 1903: A female, 30 years of age who, for one year, had attacks of paroxysmal epigastric pain radiating to the left lumbar region, accompanied by chills and fever, and the loss of about 50 lbs. Jaundice appeared temporarily nine months before admission and her stools were clay-colored for one week prior to onset of pain. She admitted excessive indulgence in alcohol. No glycosuria or evidence of biliary calculi. At operation two cysts of the pancreas, containing two stones, were found. The entire gland was atrophic and contained generally diffused calcareous material. She died the fifth day after operation. Autopsy did not reveal peritonitis but advanced interlobular pancreatitis. The Islands of Langerhans were not involved by the calcification.

Case 2. Link (10), in 1911: A female, 22 years of age, complained of paroxysmal pain in the left flank and lumbar region radiating from behind forwards and down to the pubis. She was anemic and emaciated but not jaundiced. No glycosuria, biliary calculi, or abnormal stools. She was operated upon for suspected intermittent hydronephrosis. The kidneys were normal but multiple pancreatic calculi and interstitial pancreatitis were found. Biopsy showed fine, hard white bodies about 0.5 mm. in diameter beneath the capsule of the gland. Microscopically there were areas of fibrosis in the parenchyma and many exceedingly fine calcifications in the smallest acini. The Islands of Langerhans were not involved. Recovery was uneventful.

Case 3. Bost (2), in 1931: A male, 37 years of age, had repeated attacks of epigastric colic for 25 years. In 1921 he was suddenly seized with acute epigastric pain which radiated to the back and left costal margin and was accompanied by muscular rigidity and tenderness. Roentgenograms of the gastro-intestinal tract were normal. At operation the head of the pancreas was large, indurated and grated when cut. Pus and some small calculi were evacuated. He recovered and was well until 1930 when he had another attack which subsided with treatment. On October 4, 1931, he developed cramp-like pains in the left upper quadrant, dorsal and lumbar regions, and left shoulder posteriorly, which persisted for 10 days along with some nausea but no vomiting. The upper left quadrant of the abdomen was tender on pressure but not rigid. No jaundice, glycosuria, biliary calculi, or abnormal stools. Gastric analysis was normal. Roentgen examination showed diffusion of shadows in the head and tail of the pancreas. At operation stones were palpated in the body of the pancreas, and a large mass in the tail proved to be an abscess containing stones and pus with colon bacillus odor.

The abscess was evacuated and drained. The patient recovered.

Case 4. Faust (7), in 1935: A white male, 45 years of age, with a history of alcoholic excesses. For ten years he suffered from gaseous distention, eructation, and pain in the epigastrium coming on about 30 minutes after food, passing off into a dull ache. Two years ago he had an attack of hematemesis and frequent melena. His appetite was poor. He never had jaundice, clay-colored stools, or glycosuria. He was admitted to hospital because of acute epigastric pain and tenderness simulating perforated gastric ulcer. Later, on roentgen examination, clusters of opaque shadows were seen in a widened duodenal arc and across the mid-line. A peptic ulcer or carcinoma of the pancreas with calcified glands was suspected and operation performed because of hourly attacks of severe pain. The whole pancreas was enlarged and fluctuant. Pus with a fecal odor was aspirated and the parenchyma of the gland was found to be crepitant. He died six days after operation. At autopsy the pancreas was very large and full of gravel and stones. Pus was found in a little sac between the stomach and the pancreas, which was deeply pitted at this spot. The ducts were dilated, and contained pus and several hundred stones of different sizes. Microscopic section showed evidence of progressive chronic pancreatitis with many calcified areas, reduction of the parenchyma, endarteritis, and areas of acute suppuration involving the duct epithelium.

Case 5. Chiray and Bolgert (5), in 1935, mentioned the case of a 49 year old man who had repeated epigastric crises which were accompanied by headache, slight jaundice, and subsequent anorexia and fetid diarrhea. Roentgen examination revealed generalized calcification of the pancreas. The secretin test was done on two occasions with the following results: In 1934—Volume of 27 cc. in 45 minutes, Lipase activity-2.1, Tryptic activity-0.3; in 1935—Volume of 54 cc. in 28 minutes, Lipase-4.0, and Trypsin-1.25. The authors believed that the latter figures indicated regeneration.

Case 6. Chiray, Albot and Bolgert (4), in 1935 reported the case of a patient who had several colicky epigastric crises, in one of which diarrhea, vomiting and a subicteric tint were present. Roentgen examination showed diffused calcific shadows which outlined the head and body of the pancreas more than the tail. The pancreatic fluid by means of the secretin test on two examinations, gave the following results: (1) Volume 27 cc. in 45 minutes, Lipase activity-2.1, Tryptic activity-0.3; (2) Volume 27 cc., Lipase-2.1, and Trypsin-0.

Cases 7 and 8. Gutmann and Rekis (8), in 1936, reported five cases of pancreatic lithiasis before the French Society of Radiology. Apparently two of them showed diffuse calcification of all parts of the pancreas, and one was in a diabetic. The absence of clinical data and the reproduction of only one radiograph affords us little information regarding this series.

Case 9. Pellasse and Ledru (11), in 1936, observed a 33 year old male with repeated attacks of bronchitis during the winter. He was admitted to the hospital with a diagnosis of bronchopneumonia without complaints referable to the gastro-intestinal tract. He died six days later. At autopsy a calcified gritty mass across the upper lumbar

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spine was found to be the pancreas. It was the seat of disseminated calcifications with multiple calculi in the ducts. This was further demonstrated by postmortem roentgenography. He had not suffered previously from glycosuria, jaundice, diarrhea, etc.

Case 10. Romecke (12), in 1936, gave a brief report of a male diabetic with attacks of colic in the right hypochondrium. Roentgen examination revealed calcific shadows distributed throughout the entire pancreas. His urine diastase was 61.

Case 11. Kini (9), in 1937, reported the case of a Hindu male, 39 years of age, who suffered with pain in the epigastrium for eight years, which at first began in the middle of the back and radiated to the epigastrium, but later radiated from the front to the back and lasted for a half hour or more. The attacks were not definitely related to the ingestion of food but were aggravated by lying on the right side. Jaundice, glycosuria, or diarrhea with clay-colored or fatty stools were not noted. The diastase content of the urine was 10 Units. Blood sugar—102.6 mgms. %. Roentgen examination revealed a large number of calcific shadows in the region of the pancreas and delayed emptying of the stomach following a barium meal. At operation the pancreas was uniformly hard, and glairy fluid escaped when the ducts were incised. Three large and some small stones were removed. Many smaller stones in the canaliculi were inaccessible. The duct was closed carefully around catheters inserted into it at the head and tail. After peritonectomy, the lesser sac was drained separately. The patient died three days after operation. An autopsy was not performed.

Case 12. Brook (3), in 1939, observed a man, 76 years of age, who gave no syphilitic or alcoholic history. On March 10, 1939, he had paroxysmal attacks of epigastric colic followed by collapse, which were controlled by morphine. They were diagnosed as biliary colic. Two weeks later he had a similar attack which lasted from 10 to 15 minutes. Thereafter he had them at about monthly intervals. The pain was located at a point 1 inch below the xiphoid cartilage and he felt as though fluid were being pumped into a small cavity which threatened to burst. Roentgen examination showed poor concentration of dye in the gall bladder and a mapping out of the pancreas by numerous scattered shadows. These have remained unchanged. No operation was performed. The patient has done well and has enjoyed good health without recurrence of attacks, which the author ascribed to the passage of stones through the papilla of Vater.

The following case, which has been under my observation for the past six years, may be included in this group.

#### AUTHOR'S CASE

The patient is a married man, 34 years of age, of white American stock. His father died at 53 years of age of nephritis following recurrent tonsillitis. The mother is in fairly good health except for mild diabetes which she has had for the past 15 years. One sister, 44 years of age, has fainting attacks, said to be due to some circulatory disorder. The other sister died at the age of 46 years from carcinoma of the stomach with multiple intra-abdominal metastases. The patient had measles, pertussis, mumps, chickenpox and scarlet fever in early childhood, the tonsils and adenoids were removed at the age of seven, and at twelve years he developed acute appendicitis with perforation, from which he recovered after operation and prolonged convalescence. Prior to the spring of 1934, he was in excellent health but since then his appetite has been poor, he has been nervous, constipated, and often unable to sleep. Eight years ago his weight was 165 lbs. but now averages 130 lbs. with a minimum of 120 lbs. He takes no habit forming drugs and smokes at least one pack of cigarettes daily. For the past 15 years he has indulged in alcoholic beverages to excess, ordinarily consuming about

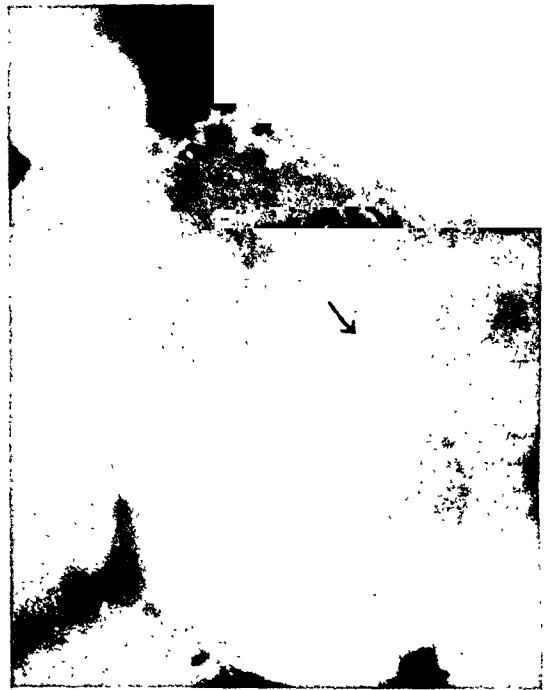


Fig. 1. Showing ulcer.

one quart of spirits a day, and at times, two quarts. In March, 1934, he began to have matutinal nausea and vomiting, often lasting days to weeks. On September 23, 1934, after his noon meal, he was suddenly taken with an acute colicky pain in the upper part of his abdomen, which lasted for 12 hours, during which time he vomited frequently. He was sent to the hospital because of the gravity of his condition. Although acute intestinal obstruction was suspected, the history of recent unusual alcoholic excess and flakes of coffee ground material in his vomitus led to the diagnosis of acute gastritis. He improved rapidly under treatment and was discharged 10 days later in a satisfactory condition. Serial roentgenograms showed the colon to be rather large and redundant in its proximal portion, the rectum and sigmoid very large and lacking in tone. Flat plates did not show any calcific shadows in the region of the pancreas.

Abstinence from alcoholic beverages and Vitamins B and C in large doses brought about a restoration of his former state of health in about nine months. Then he began drinking again and kept it up until his illness in 1939. During this time he had eight attacks of acute gastritis, violent gastro-intestinal spasms and persistent vomiting of blood stained material, as often as 50 times a day. Each attack lasted several days and was accompanied by very severe pain. As the result of his excessive drinking and persistent vomiting he became dehydrated and, on several occasions, he had visual and auditory hallucinations and epileptiform convulsions. The abdominal pains were always generalized, but were worse in the upper abdomen. During the last few attacks he also complained of severe sharp gnawing pain in the epigastric region which seemed to pierce through and be felt in the dorsal region just below the lower border of the left scapula. The attacks were all similar and cleared up rapidly under treatment consisting of fluids and glucose, large doses of Vitamin B, intravenously (20 mgms. daily), sedatives and antispasmodics. Of late the attacks have occurred once every six months.



Fig. 2

On July 13, 1939, he was seized with a sharp severe constant pain in the epigastrium, particularly on the left side, which radiated through to the back. He said that he had epigastric distress and heart-burn about 1-2 hours after meals during the preceding three months, for which he obtained relief with tincture of belladonna, bismuth subcarbonate, and bicarbonate of soda. This pain was so different from the previous attacks that he was hospitalized immediately.

He was acutely ill, with epigastric rigidity and tenderness on pressure. The lower abdomen was soft and not tender. He started to have colicky pains and excessive borborygmi while in the hospital. Intravenous 5% glucose in normal saline was commenced at once to combat the dehydration. All urinalyses were normal. The leucocytes were 9,900 with 65% polys, 1% basophiles, 31% lymphocytes, and 3% monocytes with a 17.0 nuclear index; erythrocytes were 3,800,000 with 82% hemoglobin (Newcomer) and color index of 1.0; blood sugar 96 mgms., urea nitrogen 12 mgms., uric acid 2.1, and creatinine 1.48; clotting time 4 minutes and bleeding time 2 minutes.

A diagnosis of perforating peptic ulcer was made. He improved steadily under treatment and one week later roentgen examination with a barium meal revealed a definite small niche in the greater curvature of the duodenal cap about 2 cms. distal to the pylorus, indicating a "penetrating post-pyloric ulcer" (Fig. 1). He was sent home on the 20th of September.

Four weeks later another roentgen examination showed no niche but many small discrete shadows within the curve of the duodenum (Fig. 2), which was rounded and poorly defined. The density of the shadows resembled that of calcium or of barium within the bowel. As the patient had taken bismuth for several weeks, it was possible that some of it might have leaked out into an inflammatory mass produced by a perforated ulcer. It was also possible that the shadows were due to calcium in the pancreas. On the next day he was again seized with pain in the epigastrium radiating through to the back, and was hospitalized. A

rounded mass about 3 cms. in diameter was felt on palpation of the right lower epigastrium. It was moderately tender and immobile to palpation and respiration. The biliary tract and pancreas were thoroughly investigated with the following results: Re-inspection of the first gastro-intestinal roentgenograms revealed the shadows in the duodenal arc. They had not been noticed, probably, because of the plainly visible pathology in the duodenum. Roentgenograms made of the abdomen showed a curve of miliary shadows which conformed to the outlines and position of the pancreas (Fig. 3). An attempt was then made to demonstrate the pancreas by the method of Engel and Lysholm (6) as follows:

"The method consists of taking a lateral view with the patient in the prone position, the weight supported at the pelvis and chest so that the abdomen hangs free. The patient is given an effervescent powder just before roentgenograms are made, and he drinks fluid. This distends the stomach, and the pancreas, if enlarged, projects as a shadow in the lumen of the gas-filled stomach from the posterior aspect. Roentgenograms made after this method show the miliary calcification as described previously lying anteriorly to the spine." The stomach was not indented. Fourteen and sixteen hours after he took the dye his gall bladder produced a shadow of good density, regular in outline without filling defects. It had emptied satisfactorily one hour after ingestion of fat. The head of the pancreas was clearly portrayed in all of the films by the large number of miliary calcific shadows. His blood amylase was 45.7 mgms. on August 29, 1939; 38.0 mgms. on September 1, 1939, and 36.2 mgms. on September 6, 1939. The icteric index was 6.1 and blood cholesterol, 178.5 mgms.

From the above findings a definite diagnosis of *disseminated calcification of the pancreas* was made in addition to Penetrating Duodenal Ulcer, healed. He felt well when he left the hospital on September 6, 1939. After two months abstinence, he has resumed his drinking habits and is being closely observed from time to time. The mass in the epigastrium has disappeared.

This case presents certain features characteristic of the



Fig. 3

disease. The regular excessive indulgence in alcohol and the repeated attacks of acute gastritis are important factors in the etiology of the attacks of acute pancreatitis which must have preceded the deposition of calcium. Sharp, gnawing, low epigastric pain, radiating through to the back, accompanied each attack and the intervals between attacks were symptom free. The absence of diabetes mellitus in the presence of advanced parenchymal calcification corresponds to former cases and indicates no widespread involvement of the Islands of Langerhans.

### DISCUSSION

While it would appear from the literature that disseminated calcification of the pancreas is an extremely rare disease, we lack definite proof. The rarity may be apparent rather than real if the condition goes unrecognized either from its symptomatology or roentgenological findings. So that a more accurate estimate of the incidence of the disease can be arrived at, a survey of all cases which might include the syndrome is being made and will be reported in a later paper.

### SUMMARY

All cases of disseminated calcification of the pancreas reported in the literature are presented in brief.

The 13th case is herewith reported in detail. It presents several characteristic features in etiology,

symptomatology, and roentgen and laboratory findings. Attention is drawn to the difference between pancreatic lithiasis and disseminated parenchymal calcification of the pancreas.

The apparent rarity of the disease is questioned and note is made of current investigation to determine the true incidence.

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## Ulcerative Colitis

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THE value of the case report is partly that of recording unusual experiences with an individual patient as well as the possibility of stimulating improved methods of diagnosis or treatment. Certainly this is true in so far as the physician who cares for patients who suffer from ulcerative disease of the bowel is concerned. The experiences encountered in the care of the following three patients are reported herein because we feel that they are both unusual and particularly interesting.

### REPORT OF CASES

Case 1. A man, aged fifty-three, for many years had suffered from attacks of diarrhea. Since he traveled widely, the usual diagnosis which he received was amebic dysentery; antiamebic therapy and general measures always had resulted in a slow but complete recovery. In December, 1936, he had suffered an unusually severe attack of diarrhea. A large amount of emetine hydrochloride and acetarsone had been administered with no improvement. The patient became worse and was hospitalized. Antiamebic therapy was continued, but he became more and more depleted. Finally all medication except opiates was discontinued. In about two weeks the patient had improved sufficiently to come to The Mayo Clinic (March, 1937), and he went directly to a hospital. In this three months' illness he had lost 40 pounds (18.1 kg.). The essential laboratory data were moderate secondary anemia.

leukocytosis (15,200 cells), and a sedimentation rate of the erythrocytes of 113 mm. at the end of one hour. Proctoscopic examination revealed a portion of granular edematous, easily bleeding mucosa with a large ulcer situated on the posterior rectal wall 8 cm. above the anus. The rectum was contracted to about two-thirds its normal size. It was not wise to attempt administration of a barium enema for roentgenoscopic visualization of the colon until April 26, 1937 (Fig. 1a), at which time there was observed an extensive ulcerative process involving the entire colon.

Treatment consisted in the administration of ulcerative colitis serum, but this procedure was discontinued within three days because of a severe local and systemic reaction. Ulcerative colitis vaccine was then administered and was continued for many months. The patient's diet was gradually increased to include a full high-vitamin, high-protein intake with such fruits and vegetables as he could tolerate. Occasional doses of paregoric or codeine were required to control the diarrhea. He remained under our care for two months, at the end of which he was sufficiently well to return home. He was to continue with the high protein diet, supplemented with Vitamin B and vaccine.

This patient has been examined on several occasions, the last time being in October of 1939. At this last examination he was the picture of health; in fact, the proctologic report was that he "looked as good inside as he did on the outside." He was concerned about gaining too much weight and his powers of endurance had returned to normal. The roentgenogram of the colon (Fig. 1b) revealed some residual signs of ulcerative colitis. At the moment of writing he is merely exercising good care in

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Fig. 1a. Extensive, acute ulcerative colitis, showing "fuzzy" character of the borders of the left colon; b, minimal evidence of colitis, but diverticulosis is to be noted.

selection of his food and in the avoidance of physical and nervous strain.

**Comment.** The previously described experience concerns a patient, acutely ill from ulcerative disease of the colon, whose disease subsided after the combination of rest, good food and ulcerative colitis vaccine had been utilized. He cannot be considered cured but it is hoped that the quiescence will continue indefinitely.

**Case 2.** A woman, aged fifty-nine, was admitted directly to our service at the hospital in July, 1937. She had been ill for about four weeks, suffering from diarrhea, fever and increasing exhaustion as the diarrhea persisted. She had first considered that she had "stomach flu," but as the illness persisted, she had found it necessary to come to the hospital. On admission she was having six stools daily. No blood was seen grossly in the stools. Examination of the blood disclosed mild secondary anemia. Results of tests of the stools were negative, both for parasites and for the dysenteric group of bacteria. Proctoscopic examination revealed a mucosa which bled more easily than would normal mucosa. Roentgenologic examination after administration of a barium enema (Fig. 2) was reported as showing a severe type of ulcerative disease which involved the transverse colon and the descending colon as far as the upper sigmoid. The ascending colon and the sigmoid seemed to be normal.

Treatment consisted of a high-protein, high-vitamin, low-residue diet which was supplemented with Vitamins B and C. As a supportive measure, a transfusion of 500 cc. of blood was administered. Other than administration of an occasional dose of paregoric or codeine, no other treatment was employed. On the eleventh day she was permitted to return home.

The colon of this patient was examined four months later and was found to show evidence of colitis of the right half of the colon (Fig. 3a and b), but the involve-

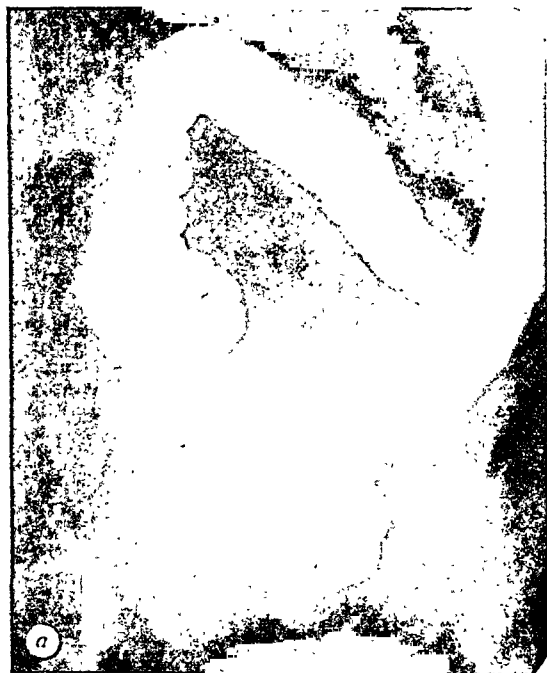
ment was minimal. It has been possible to see this patient frequently and she has continued in excellent health. She is careful to avoid fatigue and insure that her diet is well balanced.

**Comment.** This patient was seen early in the course of the colitis from which she was suffering. Simple supportive measures of good food, vitamin supplements and rest seemed to restore her to normal condition. Later, it was learned that she had been working very hard—much more so than the average individual. She had eaten hurriedly and often had taken only a "bite on the run." Hence, when intestinal disturbance afflicted her, her resistance was definitely impaired.

**Case 3.** A woman, aged twenty-nine, entered the clinic on November 21, 1938, with a two-year history of two attacks of mucoid bloody bowel discharges accompanied by cramping, rumbling and abdominal soreness. The first two attacks, which lasted three and four weeks, had been accompanied by constipation. The attack which caused her to come to the clinic had begun in April, 1938. Accompanying this attack was diarrhea, manifesting itself gradually, which was not controlled with bismuth or paregoric. She had lost 20 pounds (9.1 kg.). There was pain and redness of the left elbow. There had been intermittent fever in which the temperature sometimes increased to as high as 104° F. (40.0° C.). On admission the patient was having three or four semiliquid stools daily and one at night, all of which contained blood and pus. Two months previously a perirectal abscess followed by a rectovaginal fistula had developed. The patient was depleted, her weight having decreased from 115 to 91 pounds (52.1 to 41.3 kg.). On examination there was definite tenderness of the left elbow; the small rectovaginal fistula was noted. Estimation of the hemoglobin showed 10.2 gm. per 100 cc. of whole blood. Results of tests of the stool were negative



Fig. 2. Ulcerative colitis is manifest in the transverse and descending portions of the colon, and is more severe along the transverse colon than elsewhere.



for parasites and ova. Proctoscopic examination revealed an irregular inflammatory process involving the anterior and right walls of the rectum above the dentate margin from which, on slight pressure, pus oozed from several openings. In the sigmoid there was an inflammatory process which, grossly, was similar to that in the rectum. Part of the rectal mucosa appeared to be normal. Roentgenologic examination of the colon after administration of a barium enema (Fig. 4a and b) disclosed a marked polypoid change of the mucosa extending from the cecum to the sigmoid. The involved segment of colon suggested extensive ulcerative colitis with secondary polypoid changes.

The patient was hospitalized. A high-protein, low-residue diet supplemented with Vitamin B, was prescribed. Neoprontosil was administered in doses of 20 grains (1.3 gm.) every six hours for fourteen days. Within ten days she was passing one fairly well-formed stool a day. At the end of two weeks she was discharged and was instructed to continue her diet, restrict her activity and to take a course of neoprontosil, 60 grains (4 gm.) daily for ten days of each month.

Since her dismissal the patient has returned to the clinic twice, the last time being October 9, 1939. At that time she had gained 35 pounds (15.9 kg.). The last roentgenologic examination of her colon revealed ulcerative colitis, type 3, involving the colon from the hepatic flexure to the middle loop of the sigmoid. The involvement was sharply demarcated and still retained its polypoid character. There was a definite improvement over the condition shown by the first roentgenogram. Proctoscopic examination revealed that the mucosa had healed and that it seemed to be normal.

Comment. During the first two episodes experienced by this patient, only proctitis must have been present, because constipation existed even though she had several bloody rectal discharges each day. The last attack, characterized by greater prostration than before and also diarrhea, indicated that the disease had

E.



Fig. 3a. Minimal evidence of colitis as shown by barium introduced by enema; b, after partial evacuation of barium, residual damage is more apparent in the ascending colon and hepatic flexure.

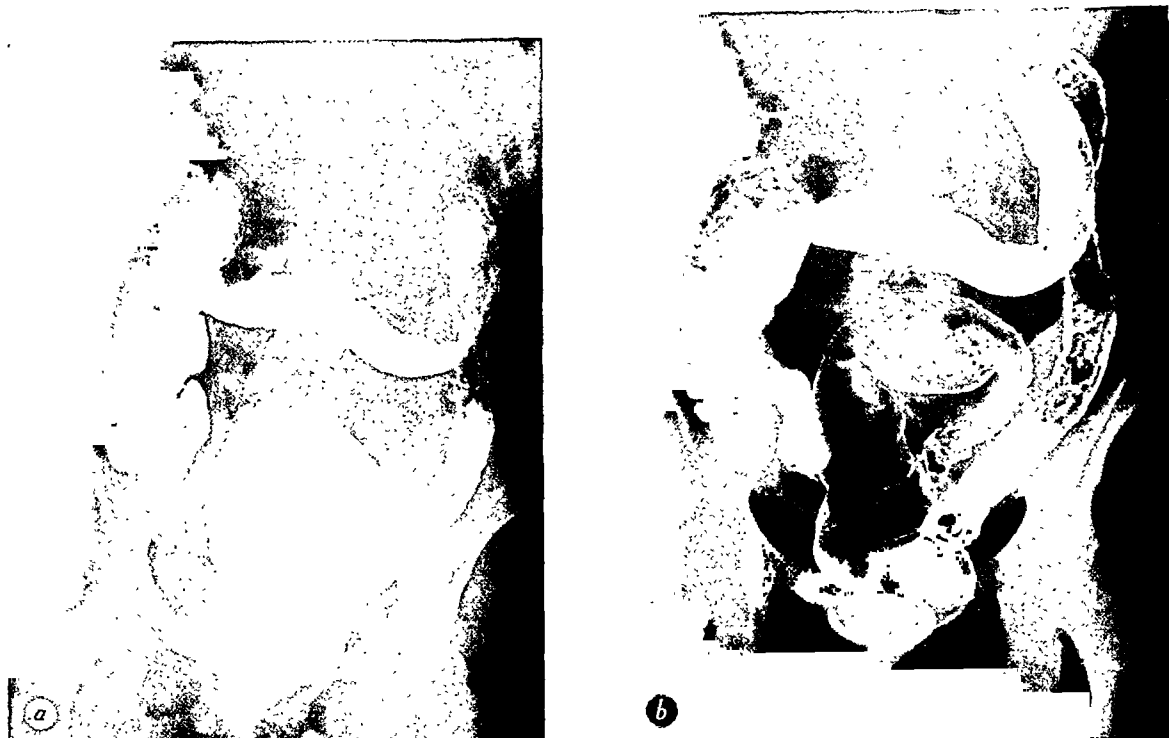


Fig. 4a. Mottling and irregularity of colon from the cecum to the sigmoid; results of barium enema after partial evacuation of barium; b, following injection of air, the polypoid features are more apparent.



Fig. 5a. Narrowing and smoothing of the colon from the hepatic flexure to the sigmoid; quiescent colitis, as shown by barium enema; b, after evacuation of barium, polypoid changes are seen to persist.



extended into the colon. The roentgenogram (Fig. 4a and b) demonstrates the severity of the process with the polypoid islets of mucosa. In this instance good food, Vitamin B and neoprontosil seemed the effective combination. This patient cannot be considered to be cured of her disease and there is the undercurrent of anxiety as to whether or not the polypoid character of the damaged colon will undergo malignant change or will resume the normal structure of mucous membrane.

### SUMMARY AND CONCLUSIONS

In so far as can be judged, the features of ulcerative disease of the colon in the aforementioned three patients have many points in common. However, the intensity and severity of the disease as it afflicted the three patients are different. If the patient in Case 2 had been permitted to continue without treatment for several more weeks, it can only be imagined what a severely damaged colon might have resulted. There is no question that the mental attitude of the patient is of tremendous value, and psychic trauma may contribute to the onset of an attack. Anxiety can do much to continue such an attack, just as anxiety can aggravate the condition of patients who suffer from duodenal ulcer. Fear of food, fear of getting too far away from the toilet, and what is referred to as "just fear"

seem to add greatly to the problem in the care of these patients.

Concerning patients who have ulcerative disease of the colon one fundamental fact is certain: their chances for recovery depend greatly on the availability of the best possible quality of food. Protein is the most important article: chiefly red meats, liver, kidneys, sweetbreads and lean pork. Unfortunately, some patients cannot tolerate pork, but for those who can, it is an excellent food and is especially rich in thiamin chloride.

Since fruits and vegetables may add too much residue to the diet and increase the number of bowel movements of the patient, restriction of these articles requires supplements of the Vitamin B group and ascorbic acid. Use of the whole Vitamin B complex, such as is now available, is preferable to the use of thiamin chloride alone. Such products are obtained from grain and may be enriched with liver. Likewise, ascorbic acid should be prescribed in doses of 200 to 400 mg. daily until such a time as the patient can tolerate orange or grapefruit juice.

We have no desire to minimize the value of other forms of treatment, all of which we employ, but we do stress the need of good food.

## Allergy of the Gall Bladder\*

### A Study Using the Graham-Cole Test and the Leucopenic Index

By

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A NUMBER of patients with allergic symptoms were found to suffer from typical gall bladder distress, after ingestion of offending foods. We had reason to believe that the gall bladder can be subject to manifestations of allergic disease and therefore undertook the study reported below.

It is known that in hay fever and in allergic reactions due to foods and other substances, not only inflammation of the mucosa of the eyes and upper respiratory tract may occur, but also of the rectal and vaginal mucosa. Recently, Gray and Walzer have supported this experimentally (1). Food allergy, like all other types of sensitization tends to manifest itself in localized reactions in selected tissue of the body, or in small areas of such special tissue (Rowe, 2, p. 63). Vaughan has drawn attention to Menkin's studies in which it was demonstrated that infection causes mobilization of the circulating antigens in the affected tissue. It is possible that infection of localized tissues, such as the gall bladder, may also concentrate allergic reactions in such areas (Rowe, 2, p. 64). Recently Alvarez has drawn our attention to association of symptoms of cholecystitis and food sensitiveness (3).

A number of patients with typical symptoms have been operated for cholecystitis without relief of symptoms, which later disappeared after offending foods had been eliminated from the diet of the patient (for literature see Rowe 2, p. 177). Shay, Cohen and Fels had reasons to believe that the gall bladder may act as a source of allergens (4). Chevallier (5) and Chevallier and Moutier (6) saw edema in the gastric mucosa of patients with dermatoses, paralleling similar processes in the skin.

In a gall bladder which was removed after the diagnosis of cholecystitis had been made, no disease was found except a mucous plug in the cystic duct; on microscopic examination of a smear of this plug, numerous eosinophiles were seen.

In allergic shock contraction of the smooth musculature occurs. In the case of the gall bladder a sudden contraction may cause distress per se, or indirectly when contraction (or swelling) of the cystic and common duct or the papilla of Vater prevent the emptying of the contracting viscus. It was decided therefore, to take cholecystograms of five patients with and without administration of offending foods and to compare the rate of emptying of the gall bladder. All of the five patients tested had a clear cut story of

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sensitivity against foods in connection with a typical gall bladder syndrome.

### METHOD

Thirty-six hours before the Graham-Cole test the patient was given castor oil. Twelve hours before he had a light, fat free supper. Four grams of sodium tetra-iodo-phenolphthalein mixed in grape juice was given 12 hours before the test. Twenty and 14 hours following ingestion of the dye roentgenograms were taken, followed by a fat meal. One and two hours afterwards films were taken again. The fat meal consisted of 3 ounces of 32% cream and 3 ounces of skimmed milk. When the patient was known to be allergic to milk, 50 cc. of olive oil were given instead. The patients were always placed in the same position on the X-ray table and a constant tube distance was employed. Following these controls, the procedure was re-

TABLE I

*Contractions of the gall bladder following motor meal with incompatible foods*

Patient No.	Per Cent Contraction			Substances Used
	At End of 1 Hour	At End of 2 Hours	At End of 3 Hours	
1 I.S.	43	58		Control, milk and cream
	40	67		Banana powder in milk and cream
	46	67		Banana powder in milk and cream
	52	69		Cocoa in milk and cream
2 C.S.	41	44		Control, olive oil
	48	66		Milk and cream
3 E.K.	26	41		Control, milk and cream
	45	63		Cocoa in milk and cream
4 L.B.	36	46	59	Control, milk and cream
	38	43	60	Egg white and milk and cream
5 R.R.	40	66		Control, milk and cream
	48	43		American cheese in milk and cream
	75			Casein in milk and cream

peated, but a small amount of the offending food was given with the motor meal. The tests were performed once a week, consecutively. The films were placed on a horizontal shadow box and the surface area of the gall bladder was measured with a planimeter; each value represented in Table I is the average of 3 readings. The size of the gall bladder on the 14 hour control film was taken as standard, and contraction of the organ expressed in per cent decrease of the gall bladder shadow relative to the standard. Only such patients were employed in whom X-ray showed normal stomach and duodenum and whose gall bladder concentrated the dye and showed no stones. The symptoms following offending foods were: pain in r.u.q., often radiating to interscapular space; tenderness in the region of the gall bladder; nausea, heaviness in epigastrium, shortness of breath, sneezing, headaches, belching, coated tongue, hives and itching. The first two symptoms occurred in all patients, the latter ones in a great number of tests when the foods to which the patients were sensitive, had been ingested with the motor meal. All patients were tested endermally in the Allergy Clinic. The offending foods in each case gave positive reactions. Proof of their clinical importance was obtained by administering the

offending food during symptom free periods. This was done at least on four different occasions at intervals of a week or more. In all trials symptoms could be produced that were attributable to the suspected food. All patients were females, their ages ranging between 25 and 41 years.

### RESULTS

Patient No. 1 was clinically sensitive to banana and cocoa. Two hours following the ingestion of a teaspoonful of either of these, the gall bladder had contracted approximately 10% more than in the milk and cream control. Patient No. 2 was allergic to milk. Olive oil was used as the control motor meal. In the following test a milk and cream motor meal caused the organ to contract 22% more than with olive oil. This is more significant since we found in a series of normals tested for control purposes, that 50 cc. of olive oil is a more effective motor meal than one of milk and cream. Patient No. 3 was clinically sensitive to cocoa, one teaspoonful of which was followed two hours later by a 22% greater emptying of the gall bladder. In patient No. 4 ten drops of egg white produced typical and severe distress, but no change in the rate of emptying of the gall bladder.\* In patient No. 5 ingestion of a thin slice of American cheese with the motor meal produced very severe symptoms, and the patient refused to have another film taken. The gall bladder contracted 23% less than in the control. This patient had been found (by skin tests) to be highly sensitive to casein. Ingestion of milk and cream did not produce discomfort. When 2 teaspoons of casein had been added to the milk and cream meal, she had a violent attack with general and gall bladder symptoms, and the viscus contracted 35% more during the first hour following ingestion, than after milk and cream only. Due to the condition of the patient no film was taken at the second hour.

From the above results it appears that besides general symptoms and typical gall bladder distress, allergenic foods may produce a disturbance in the emptying of the gall bladder. This was manifested by faster emptying in 6, and in delayed emptying in one, out of 8 tests performed. In one patient no change was noted, although considerable pain and tenderness was present in the region of the gall bladder.

We are well aware of the shortcomings of the method employed. It was not possible, however, to induce the patients to undergo more tests, even control tests without an offending food, following the great discomfort the previous tests had given them. The 14 hour values for the size of the gall bladder before the motor meal checked closely in the different tests and this made us feel that we were justified in comparing the values obtained in the control with those following the various meals. We did not employ the excellent quantitative method developed by Boyden (7) because we were interested in the end points rather than in the configuration of the curve of emptying of the gall bladder. Films of the gall bladder were taken in a few patients at shorter intervals, but did not furnish additional information. The configuration of the gall bladder was the same on all films, so that a flopping over of the viscus, etc., as observed occasionally, could be excluded. We may conjecture that in patients 1-3 and 5 (casein) in whom faster emptying was observed

\*Egg white by mouth without the motor meal did not affect the size of the gall bladder in this patient, although considerable epigastric distress occurred.

the allergic insults were localized more or less in the gall bladder. In patient 5 whose gall bladder emptied less following the ingestion of cheese, the assumption may be made that the site of action was more or less in the cystic or common duct, or in the sphincter of

Oddi. An indirect proof for this may be seen in the interesting experiments of Deissler and Higgins (12) who found that in anaphylactic shock in the guinea pig the sphincteric resistance was greater than the maximal pressure of the gall bladder. We are, of

TABLE II  
*Leucopenic indices in patients with food allergy*

No.	Patient Sex	Age	Incompatible Foods	Gall Bladder Pathology	Experimental Procedure	Dis- tress	+ Variation of W.B.C. Within 2 Hours p.c.	Skin Tests* (Intradermal)
1	F	42	Cantaloupe Banana Sweet corn Fried foods	Poor dye concen- tration. Several radio-translucent calculi	Fasting Cantaloupe Cantaloupe 1 mo. later Sweet corn Milk and cream Egg fried in butter Cucumber Bananas	— +  ++ + + + +	+1800 +2000  -2600 -900 -1850 +2000 +2100 -2100	Artichokes + Banana ++  Endives ++
2	F	16	Starchy foods Sweets Tomato Butter	Poor dye concen- tration	Fasting Dill pickle Tomato soup Rhubarb Milk and cream	— + ++ ++ ++	-500 +500 +800 -2400 -600	Orange + Pistachio + String beans + Rhubarb ++ Lima beans ++
3	F	28	Peanuts	Fair dye concen- tration. A No. of radio-translucent calculi	Fasting Strawberries Bananas Peanuts Milk and cream Fried egg Rice steamed	— — ++ + (+) — ++	+500 -1900 +2100 -4300 -1700 -900 -1700	Horseshoe + Mustard + Strawberries + Peas + Banana ++ Rice ++
4	M	58		Poor dye concen- tration. Calcific shadow	Fasting Pens steamed Black coffee  Fried egg Milk and cream	— + +  ++ —	-1000 -3100 +2000  -2400 +3600	Banana + Strawberries + American cheese ++ Clams ++ Allspice ++ Cloves ++ Dill ++ Pens ++ Celery ++ Parsnip ++ Grapes ++
5	M	56	Milk Butter Navy beans	No dye concen- tration	Fasting Navy beans steamed Bananas Milk and cream	— + — +	-600 -1400 -1800 -2200	Banana +
6	F	37	Milk Applesauce Bread Fats	No dye concen- tration	Fasting Milk and cream Dill pickle Applesauce Egg fried in butter Banana	— ++ ++ ++ ++ ++ ++	+2000 -3400 -3000 +1000 +1100 -1400	All tests negative

\*Only positive tests are quoted.

— Belching, nausea, sour taste, hicough, bloating.

++ Belching, nausea, sour taste, hicough, bloating and epigastric distress.

course, cognizant of the fact that in our subjects atopy rather than anaphylaxis is present. It would be merely speculation to try to explain why patient 5 could tolerate casein when administered as milk but had severe symptoms when ingesting it as purified casein.

As a further measure to establish a connection between gall bladder attacks and allergenic foods, the leucopenic index was used. This method, an application of Vidal's liver test, was introduced by Vaughan in 1934 (8). We followed closely the methods elaborated by him and by Rinkel and Gay (9). Objections raised by Sabin and collaborators (10) have not been substantiated by Jones and collaborators (11). The leucopenic index is not specific for gall bladder or liver dysfunction because persons manifesting acute allergic symptoms of any type due to food allergy may show a leucopenic response. We are presenting only cases with normal stomach and duodenum (confirmed by X-ray) whose symptoms after eating offending foods were those of gall bladder distress. In all of them cholelithiasis or cholecystitis were shown to be present by X-ray, and previous attacks of jaundice were reported by some of the patients. In addition skin tests and exclusion diets had proved sensitivity to the foods employed in our procedures. Six patients were tested. On different days the following routine was performed: leucocyte curve during fasting, and following ingestion of a number of foods. The distress which occurred following the eating of offending foods was in all respects similar to that described above in the patients whose gall bladder function was tested.

A study of Table II reveals interesting facts: Firstly, distress following ingestion of non-compatible foods is in no constant relationship to the drop of the leucocyte curve. This is brought out particularly in case No. 5, in which ingestion of all foods was followed by a drop of the leucocyte count, while distress occurred only with navy beans and milk and cream (see Fig. 1).

Case No. 6 (Table II) illustrates this point equally well.

Secondly, the results of skin tests, the occurrence of distress and drop in the leucocyte curve do not parallel each other regularly. In Table II only positive tests are recorded, but the endermal tests had been fairly complete (over 200 skin tests were performed on each patient).

Thirdly, foods which the patients pointed out as incompatible usually were followed by distress, but the leukopenic index and the results of skin tests did not parallel the distress regularly. We are aware of the fact that in the above experiments a number of foods do not react on the gall bladder solely or at all through allergic reactions, but through physiological mechanisms (gall bladder contraction through a humoral or intraduodenal mechanism, etc.). This complicates the interpretation of the leucopenic index and of the skin and diet exclusion tests.

An interesting fact observed in the experiments on leukopenic index deserves mention: whenever a patient suffered great distress following ingestion of a food, and when his leucocyte count had dropped considerably, disappearance of the distress was followed by a rise in the leucocyte count. In view of the complicated mechanism of the leucocyte shift from the skin to the internal organs of the body, it remains an open

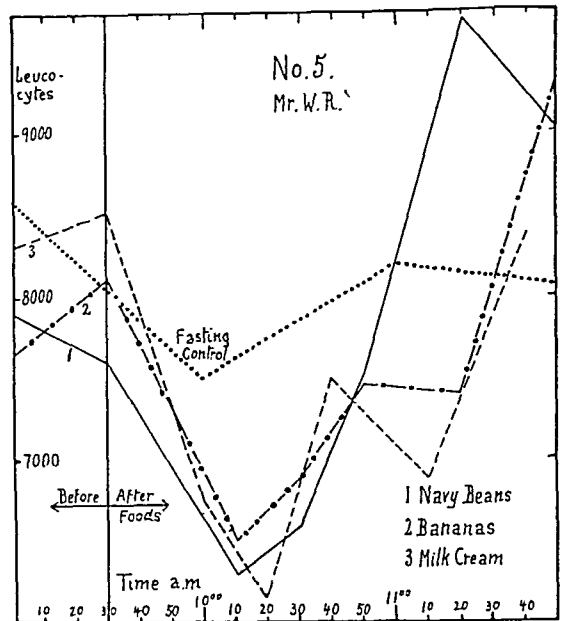


Fig. 1. Leucopenic index of patient No. 5, Table II.

question whether or not apprehension and pain may not per se produce a drop of the white count, independent of other factors.

## SUMMARY AND CONCLUSIONS

Patients suffering with allergic symptoms and gall bladder distress were examined. In 5 patients the gall bladder shadow (on the X-ray film) following a motor meal was compared with that following a motor meal which was incompatible or to which a small quantity of incompatible food had been added. In 6 out of 8 tests faster emptying of the gall bladder occurred after ingestion of offending foods.

The leucopenic index was compared to the symptoms of distress, skin tests and results of exclusion diets. While in a number of experiments all three tests agreed, no constant and regular relationship could be found.

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## The Gastrosopic Inspection of the Pylorus\*

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THE use of gastroscopy as a routine diagnostic method in abdominal diseases has become so widespread and the technical limitations of the method are so well recognized that it seems important to emphasize its possibilities. All observers agree that there are so called "blind areas" present in the stomach, areas usually not seen at gastroscopy. These are: 1. The lesser curvature of the antrum or a part of it. (Cases in which the entire antrum is seen are not frequent, but they occur. Borland's (1) opinion on this matter is perhaps too optimistic). 2. That portion of the posterior wall on which the instrument lies. In some cases, however, this region may come into view also. These areas are important and the frequent impossibility to see them usually prevents gastroscopists from making a definite negative diagnosis of a localized disease. 3. A segment of the greater curvature on which the tip of the instrument slides. No lesions have been overlooked thus far, so far as we know. 4. Some observers claim a blind area in the fornix, in the supradiaphragmatic portion of the body of the stomach. We believe that with a proper technique this region is usually well seen.

It is much more important to know that in the average patient all other portions of the stomach can be seen, in all types of constitutions. It becomes evident from a review of the literature and from personal observations of the senior author that many workers are not yet able to grasp all the possibilities offered by the flexible gastroscope. The most certain criterion for a complete observation of the stomach is the visualization of the pylorus, which frequently requires a great degree of skill. Henning (6) has contended that pathology of the pylorus not diagnosed otherwise is rarely encountered. But this is not the salient point. The observation of the pylorus will convince the observer that he has seen everything that can be observed gastroscopically. There are, however, cases in which the pylorus cannot be seen even with the best technique and the best cooperation of the patient. However, if the angulus is not seen then the gastroscopic examination, in our opinion, should be considered unsatisfactory. The "angulus" is that part of the stomach where the lesser curvature suddenly changes its direction turning cephalad. It does not correspond necessarily with the "incisura angularis," seen at X-ray, from an anatomical viewpoint. Ulcers lying at fluoroscopy some centimeters above the "incisura angularis" are found to be at the "angulus" at gastroscopy, so that the turning portion of the lesser curvature is probably not a fixed point anatomically. However this may be the "musculus sphincter antri," marking the

entrance of the antrum, is usually seen at the level of the angulus. If the antrum is seen the gastroscopic examination can be considered successful, and therefore seeing of the angulus is of decisive importance. This has not always been so. In the years of the rigid gastroscopes (1881-1932) it was frequently impossible to find the angulus. This occurred in half of all cases. Immediately after the construction of the flexible instrument it became evident that the pylorus was seen with the greatest of ease in patients in whom previously it had never been observed. The reason for this change was that the rigid instruments were frequently not able to stretch the posterior wall of the stomach so that a view of the distal portion of the organ was impossible, whereas with the flexible instrument such stretching is not necessary because the gastroscope itself bends along the posterior wall. Gutzeit (4), however, comparing the rigid Korbisch gastroscope with the flexible instrument, came to entirely different conclusions. He believes that the pylorus is sometimes better seen with the rigid gastroscope, and at other times with the flexible one. This opinion is in full contrast with the experience of the senior author, and can be explained only by insufficient utilization of the possibilities offered by the flexible instrument. The only available figure concerning the use of the rigid Korbisch instrument is that of Thorlakson (15) who found the pylorus in only 55% of his cases, a figure which is in full accord with all former experiences with the rigid gastroscopes and below all figures published with the use of the flexible gastroscope. Only few authors give clear statistics. Schloss (13), Dockeray (2), Taylor (14), Gölzow and Afendulis (3) state that they saw the pylorus in 90% of all cases, using the flexible gastroscope. Kirschen's (8) figure is 80%. Other authors state that the antrum and the pylorus are more easily seen with the flexible than with the rigid gastroscope (Henning (5)) or that the pylorus is brought into view more or less easily (Moutier (10)). A close observation of the literature as well as of gastroscopic work shows, however, that such good results are relatively rare. This becomes obvious if we consider more elaborate statistics and this fact explains the lack of precise data in many introductory papers. Moersch (9) was surprised to learn that other observers had been experiencing such great difficulties in the examination of the antrum, when he himself had been phenomenally lucky in the examination of this portion of the stomach. It is unnecessary to point out that this is not a matter of luck, but one of technique. The two best statistics on the problem of seeing the pylorus are those of Kirihaara and coworkers (7), and those of the excellent introductory paper of Royer and coworkers (11). Kirihaara

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saw the pylorus in only 70% of 292 cases in spite of the fact that he used a special tip in order to improve the possibility of inspecting this part of the stomach. Royer saw the antrum (not the pylorus) in only 62.2% of 312 cases. Thus we can assume that the pylorus is seen by the average observer in 60 to 70% of all cases. This figure is too low, as we shall endeavor to demonstrate, and it can be improved by proper technique and good training. Schloss (13) believes that the retrograde system of Henning (6) gives the best results. This system has been tried by the senior author for a long time (12). The retrograde optical system does not facilitate the finding of the pylorus; it increases the blind area of the greater curvature (see above) so much that this instrument is no longer manufactured.

Our own experiences are as follows: When we became aware of the problem, we decided to incorporate in every gastroscopic report a statement as to whether or not the pylorus was seen. Since there are always a number of observers present at our examinations, there has seldom been a case in which the pyloric activity has not been seen by several observers. Our figures are based on 348 gastroscopic examinations of new patients only, performed during recent months. In four (1.1%) of these cases the gastroscopic examination was impossible because of obstruction of the cardia or lack of cooperation of the patient. In 8 cases (2.3%), the examination could not be continued because of poor cooperation, and was reported as unsatisfactory. There remain, therefore, 336 cases in which the gastroscopic examination was considered satisfactory. In 21 of these, there were anatomic or pathologic conditions present which prevented the pylorus from coming into view, namely:

Resected stomachs .....	3
New growths obstructing the pylorus....	10
Adhesions due to pyloric disease.....	6
Diaphragmatic Hernia .....	2

In one case food filled the antrum, and in another case we decided to disregard the pylorus because of the presence of disease in the upper portion of the stomach which required our full attention. There remain, thus, 313 cases in which the pylorus should have been seen. In 28 of these (8.9%) the pylorus could not be seen. Thus the pylorus was demonstrated in 285 (91.1%) of the 313 cases. If we compare the number of cases in which the pylorus was observed with the total number of new cases examined, we find that the pylorus was seen in 91.7%. This percentage will be reduced to 85% if we include all the cases which were omitted. However, it seems to us that it is more logical to disregard all those cases in which for obvious anatomical or pathological reasons it was impossible to see the pylorus, because the number of resected stomachs, carcinomas, etc., will vary in different clinics or hospitals and therefore the addition of these cases must necessarily confuse the statistics.

We by no means contend or claim that our figure of 91.1% is the best one that can be attained, but we believe that gastroscopic technique cannot be considered adequate if the pylorus is not observed in at least 80% of all cases in which it should be possible to see it.

This result can only be attained by adequate technique. The most essential point is to avoid spasm of the stomach. This is accomplished by a good psychological preparation of the patient and by skillful introduction of the gastroscope. Psychological preparation

is particularly important in new patients especially those referred by other physicians. The gastroscopist should not start anesthesia without having discussed with the patient his particular symptoms, considering carefully every complaint and trying to bring out why in his particular case this examination is important. Furthermore, the patient should be reassured that the examination is extremely easy if he will cooperate. The usual answer is: "I will try to do my best," and the reply should be, "Nobody can do more, and if you do this, the examination will be very easy." The atmosphere depends largely on the nurses. Every word which may suggest a major procedure should be avoided, a gay environment should prevail, and even jokes are permissible. They will convince the patient that nobody in the clinic considers gastroscopy to be an exceptional or serious procedure. It is important to consider the place of birth and education of the patient. It is proper to explain everything to be done to a patient who has been educated in the United States. He will appreciate it if he is told in advance that the feeling of numbness which develops as a result of the application of anesthesia to the throat, may be disagreeable. Patients with European education are often inclined to exaggerate their discomfort. To them short though friendly commands give good results. Gastroscopy should not be carried out in an operating room. We physicians usually are unable to imagine how tense the most cooperative patient becomes when he sees himself within the walls of the surgical amphitheater, with the clean and shining tiles, the complicated operating table, the instrument cabinets and the smell of anesthetizing agents. A simple office should be used. The preliminary introduction of an Ewald tube should be followed by the explanation that the other tube through which the stomach can be seen has exactly the size of the Ewald tube, but that its upper end is stiffer and that therefore the patient may experience some disagreeable pressure in his throat which the examiner promises to avoid if possible. The patient is told that he must not move the right shoulder or the left elbow because by doing so he will surely cause the picture to disappear. The examiner himself will proceed to show the patient the proper position. It is only through this method of approach that we can gain the patient's complete confidence and prevent the development of spasm.

A wrong technique in the introduction of the instrument may destroy everything one has done in the way of obtaining a well relaxed and cooperative patient. Most patients become stiff when the instrument is introduced in a well lighted room. Only a green light is permissible. The flexible gastroscope in contradistinction to the rigid instruments should never be introduced with the head extended. Full advantage should be taken of the flexibility of the instrument. At the beginning of its introduction the instrument should be perpendicular to the long axis of the body or even slightly less than a right angle, being pointed slightly cephalad so that neither the metal of the tip nor the rubber cover of the flexible portion will touch the teeth. The instrument should be swept through the 90-100 degree angle and into the axis of the body only as the rigid part approaches the teeth. The tip of the instrument will be in the stomach before the patient has had time to realize that its introduction has been

made. At this moment the patient should be reassured with statements such as: "We are in the stomach; it was very easy; we are seeing everything; do not stop breathing," etc.

The chief technical point, however, concerns the speed of the introduction. The constrictor muscle of the pharynx should be passed slowly while the patient is swallowing, but from here on speed is desirable. A rapid introduction is essential. After the passage of the constrictor of the pharynx not more than 1 to 3 seconds should elapse in introducing the tip of the instrument down to the lower depths of the organ. No force is needed to attain this goal for the instrument will slide down readily and swiftly. No danger is involved in this rapid procedure, no resistance is encountered at the cardia and no spasm develops. If, on the contrary, slow introduction is carried out then the patient may develop severe spasm and poor results will be obtained. There are some cases in which a spasm of the posterior wall or a circular spasm of all of the stomach will develop in spite of rapid introduction. The pictures observed are characteristic; either a protruding thick fold of the posterior wall is seen casting a shadow on the anterior wall, or a circular contraction appears in the visual field which is frequently confused by the beginner with the "musculus sphincter antri." If such a spasm develops the examination becomes difficult, but still an excellent exploration can be carried out if the proper technique is followed. The thing to do is to wait and to try to divert the patient's attention. This can be done only by talking continuously, not advising the patient to relax (this will tend only to increase his tenseness) but describing the picture obtained or seen to the assistant or the observers. The patient will become interested and all his tenseness will disappear, and suddenly the spasm will be gone and the instrument will slide down into the lower depths of the stomach. At times we have been compelled to wait four or five minutes before being able to see the antrum, but in only eight of the 313 examinations did we classify the examination as unsatisfactory because of inability to see the angulus and the antrum.

When the antrum is located the seeing of the pylorus is usually easy if the examiner is patient and waits until the antrum springs into action. These contractions of the antrum are frequently seen immediately

but at times one has to wait for several minutes before they start. In spite of the fact that the patient is experiencing very little discomfort these few minutes will be almost unbearable to him if his attention is not constantly diverted by a concise, comprehensive and emphatic description of the picture observed. The appearance of the angulus, musculus sphincter antri, mucosa of antrum, etc., should be fully described and the observation of the first small peristaltic wave should be greeted with audible enthusiasm. Then the patient will cooperate and the pylorus will become visible in most of the cases, 91.1% in our series, as previously described.

#### SUMMARY

1. Faulty technique may discredit the endoscopic examination of the stomach with the flexible gastroscope.
2. The possibility of seeing the pylorus is the most important single criterion of a good, successful gastroscopic examination.
3. In our series the pylorus was seen in 285 (91.1%) of 313 cases in which it should have been seen.
4. Gastroscopic technique should not be considered satisfactory if the pylorus is not observed in at least 80% of all possible cases.
5. The technique for the finding of the pylorus is described.

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## An Improved Routine for the Roentgen Examination of the Rectum and Sigmoid\*

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THE lower portion of the large intestine is a common site for malignant neoplasms. Six per cent of all carcinomas are located in this region. Of intestinal new growths, seventy-seven per cent are

found in this part of the large bowel. Many of these lesions give characteristic symptoms and signs which lead at once to a correct diagnosis. Others are insidious in onset and in the early stages give clinical signs indistinguishable from toxic or functional disorders. From this latter group, patients are frequently

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Submitted February 22, 1940.

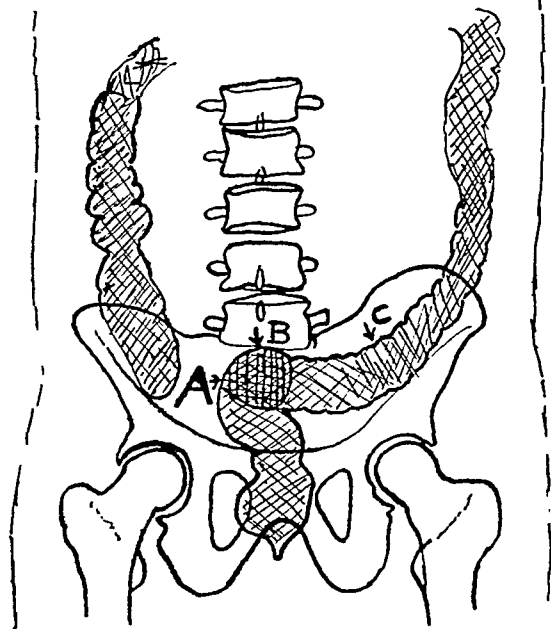


Fig. 1. Antero-posterior film showing good visualization of proximal sigmoid (B-C) and obscuration of distal sigmoid (A-B).

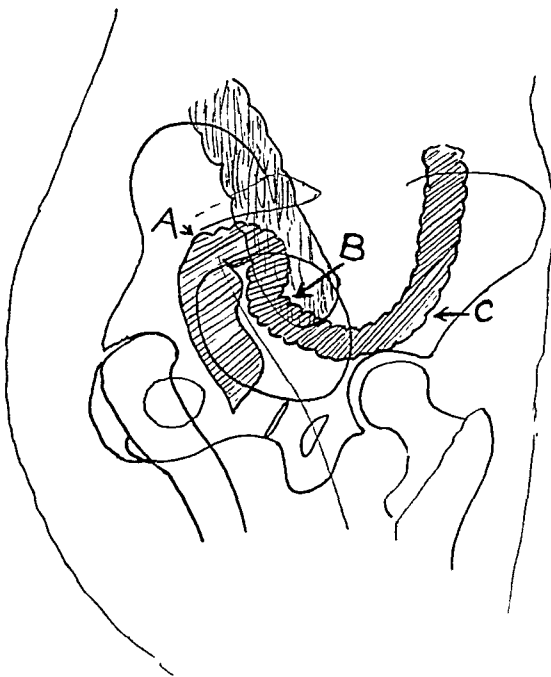


Fig. 2. Right anterior oblique film. Both the distal sigmoid (A-B) and the proximal sigmoid (B-C) are visualized. Note also that cecum may cause obscuration in this view.

referred to the roentgenologist for the purpose of ruling out malignant disease. If, under these circumstances, an erroneous negative diagnosis is rendered, a patient is likely to be treated symptomatically for a long period in a manner prejudicial to chances of a permanent cure. The hope of control of carcinoma of the sigmoid and rectum is dependent on early recognition and prompt treatment. It is therefore obvious that the roentgenologist has a great responsibility and should use every means at his command to avoid error.

Some years ago, one of the authors of this paper brought out the fact that an oblique view is necessary

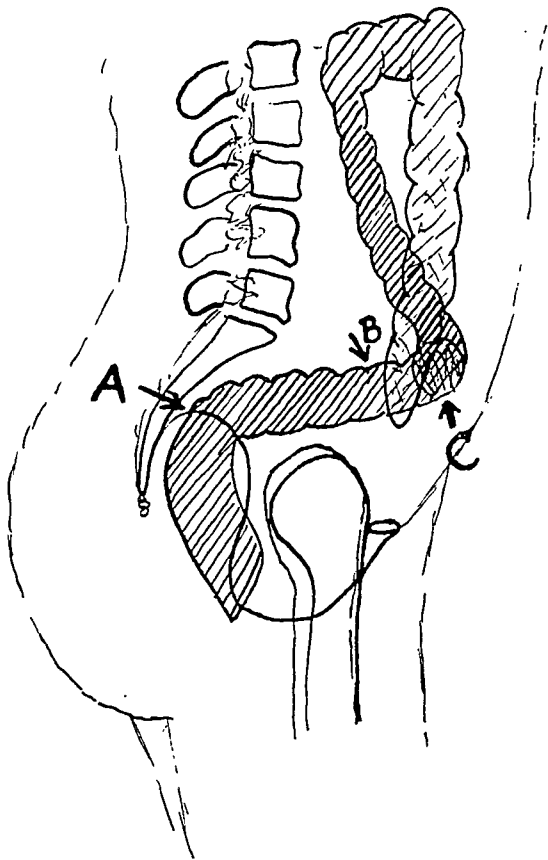


Fig. 3. Left true lateral film. Rectum and distal sigmoid (A-B) well visualized. Proximal sigmoid (B-C) obscured. Cecum seldom causes overshadowing in this view.

to visualize certain sigmoid lesions which may be completely obscured in the prone and supine positions. The routine use of this projection has permitted a positive diagnosis in a large number of cases and amply justified the claims made for its use. Since then we have supplemented the oblique position with a true lateral projection. This projection was described by Robbins and Altman in the American Journal of Roentgenology and Radium Therapy in October, 1938, and they stated that it had been previously used by Kantor and Fricke. The main purpose of this paper is to emphasize the importance of this diagnostic procedure and to urge its adoption as a routine view in the examination of the large bowel. The anatomical



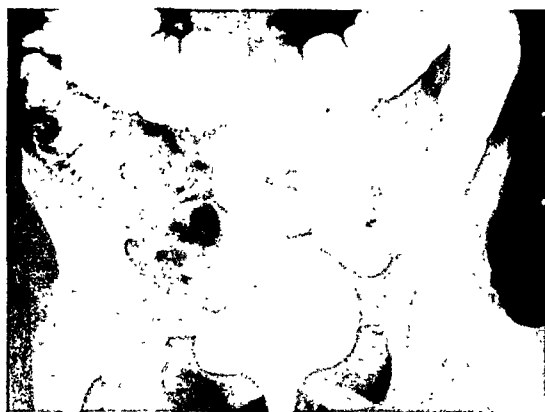


Fig. 4. Case 1. Antero-posterior view. Non-visualization of tumor.

considerations, particularly of a true lateral film of the colon, are of extreme importance and will be considered at some length. With the patient lying in the supine position the rectum is far posterior, its dorsal wall lying in the hollow of the sacrum separated from it by a very narrow band of tissue. The upper portion of the rectum and the recto-sigmoid junction are more anterior but still deep in the pelvis. The distal sigmoid, for a distance of two to six or even eight inches, lies with the lumen in an antero-posterior axis which passes from the hollow of the sacrum almost directly forward toward the anterior abdominal wall.

These points should be kept in mind when viewing films of the colon made in the various position. Figs. 1, 2 and 3 show schematic diagrams of the rectum and sigmoid as seen in antero-posterior, right anterior oblique and left true lateral positions. In all three of the sketches the recto-sigmoid junction is indicated by letter A. The mid sigmoid is indicated by the letter B and the junction of the descending colon and sigmoid by the letter C. In Fig. 1 it can be seen that points A and B are more or less directly superimposed and the distal sigmoid thus obscured. B and C are well separated

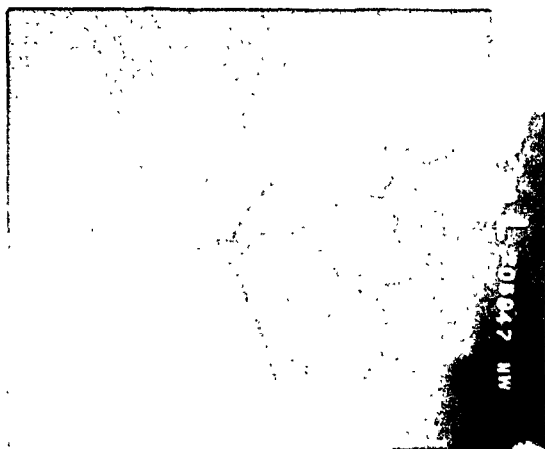


Fig. 5. Case 1. Right anterior oblique view. Non-visualization of tumor.

rated and the proximal colon clearly demonstrated. In Fig. 2 points A, B and C are fairly well separated and the outline of both proximal and distal sigmoid obtained. In this view the visualization is somewhat tangential and consequently a small lesion in either the proximal or distal sigmoid may be obscured. There is a tendency for the cecum to interfere in this projection if the entire colon has been filled before the films are taken. Another point to be noted is the fact that the anterior and posterior walls of the rectum are not seen in profile. In Fig. 3, the true lateral projection, points B and C are superimposed indicating obscuration of the proximal sigmoid. However, A and B are well separated in this view and lesions of the



Fig. 6. Case 1. True left lateral view. Carcinoma of the anterior wall in the recto-sigmoid region. Well visualized.

distal sigmoid and of the anterior and posterior walls of the rectum can easily be made out.

These three views of the lower bowel are, in our opinion, mutually supplementary and necessary in all cases. The antero-posterior view is the only one in common use. The right anterior oblique film is most satisfactory if it is made during fluoroscopy because with complete filling of the colon the cecum often superimposes and causes obscuration of a portion of the sigmoid. To be satisfactory, it should be made during the actual introduction of the barium, otherwise incomplete filling will probably result.

The taking of the left true lateral view of the rectum and sigmoid may be deferred until after complete filling of the colon, as in this position the cecum is thrown forward and does not interfere with the view of the sigmoid. Satisfactory films can usually be ob-



Fig. 7. Case 2. Postero-anterior view. Non-visualization of lesion.

tained in this position, with exposure factors of 75-85 KVP, 50 MA and 10 seconds with a target film distance of 30 inches. In extremely heavy patients the tube may be brought down to 25 inches.

Films of two cases are shown which illustrate the value of the true lateral position. Figs. 4, 5 and 6 show a case with a carcinoma of the anterior wall of the recto-sigmoid junction. It is not shown in the antero-posterior and oblique views but is well visualized in the true lateral. Figs. 7, 8 and 9 show a carcinoma of the posterior wall of the recto-sigmoid region.



Fig. 8. Case 2. Right anterior oblique view. Non-visualization of lesion.



Fig. 9. Case 2. Left true lateral film. Carcinoma of the posterior wall in the recto-sigmoid region demonstrated.

This also is only satisfactorily visualized in the true lateral projection.

In order to satisfactorily diagnose lesions of the sigmoid and rectum a barium enema should be administered under fluoroscopic control. The observer must be well accommodated for fluoroscopy and should look for any deformity in the lumen or any hesitation in the upward progress of the barium column. Observations must be made in both the right and left oblique positions as well as in the antero-posterior position.

During the introduction of the barium "flash" or "spot" films should be made in the right anterior oblique position. After complete filling films are taken in prone and supine positions and a film of the pelvic colon made in the left true lateral position.

After evacuation a single prone film is made. This is to be augmented by films in other positions as indicated by the position of any suspicious area.

If a conclusion cannot be reached after this procedure the colon should be filled with air and further films taken.

# Influence of Raw Banana and Apple Upon Disappearance of Complex Carbohydrates from the Alimentary Tracts of Normal Children \*

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IN the practice of dietetics and nutrition emphasis is usually placed on intakes of protein, carbohydrate, and fat moieties, and such mineral elements as calcium, phosphorus, or iron. Other equally important though less familiar constituents (1, 2) are often disregarded. It has been demonstrated that substitution of equal quantities of banana for apple in the diet may not change the quantity of the total residue (fiber) but the proportion of the lignin, cellulose and hemicellulose may be significantly altered and these may in turn augment or retard the utilization of nitrogen and other elements (2). The same food substitution may not significantly change the average daily alkaline- or acid-ash intake per kilogram of body weight but the proportions of the individual basic and acidic mineral elements may be greatly altered, producing a change in the trend of metabolism (1) as growth proceeds.

The physiologically beneficial effects of cellulose (3-6) and, more recently, the recognition of the component parts of "crude fiber" in satisfactory elimination have gained dietetic consideration (7-15). Mangold (10) has defined crude fiber as "the sum of all those organic components of the plant cell membrane and supporting structures which in chemical analysis of plant foodstuffs remain after removal of crude protein, crude fat, and nitrogen-free extractives." It is composed of a mixture of chemical substances, cellulose, hemicellulose (pentosans, hexosans) and encrusting substances (lignin, cutin, suberin, pectins), knowledge of whose chemical, physical and structural properties is most incomplete. No enzymes in man's digestive tract capable of digesting cellulose and its associated polysaccharides have been found, hence, these substances are sometimes spoken of as "unavoidable carbohydrates" (14). The digestibility or disappearance of fiber from the digestive tract of man is extremely variable and depends in part upon its content of cellulose and pentosans, lignin apparently not being digested at all, and the presence of bacteria in the alimentary canal. The young non-lignified cell membrane of plant foods is much more easily broken down by bacteria than older, lignified structures, consequently the disappearance of indigestible carbohydrates from the digestive tract varies inversely with the lignin content of the intake.

By determining the caloric value of the food intake and the corresponding feces and their contents of water, nitrogen, total fiber, and its constituent complex carbohydrates (lignin, cellulose and hemicellulose) it is possible to ascertain how much decomposition has taken place during the food's transit through the alimentary tract. Moreover, the laxation rate in relation to the composition of the stool and the water intake provide an index to the type of elimination consequent

TABLE I  
Diet alterations

	Content of Diet During Pre-experimental Period		Changes in Diet During Experimental Period			
	Apple (gm.)	Banana (gm.)	Addition		Deletion	
			Food	(gm.)	Food	(gm.)
Group I: H.H., F.C., D.P.	100	100	Banana	100	None	
Group II: P.S. B.M. J.H.	100	100	Banana	100	White bread Cereal*	10 20
Group III: J.M., B.F.	200	none	Banana	100	White bread Cereal*	10 20
Group IV: P.W.	100	100	Banana	100	None	
			Potato	30		
			Butter	10		
			White bread	50		

\*Shredded wheat or corn flakes.

to a particular intake. The present study is concerned with the metabolic effect of altering the proportions of apple, banana and cereal in children's diets upon the disappearance of "unavailable carbohydrates" in their digestive tracts and the resultant influence upon the growth and well being of the subjects.

Lignin, cellulose and hemicellulose in the food and feces were determined by the method described by Williams and Olmsted (7) with but minor changes (2) which were necessary to meet laboratory conditions at hand. The method has given reproducible results under the conditions of this experiment and although the separation and determination of cellulose

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and hemicellulose is not precise, it does yield values superior to those obtained by the time-worn method of Weende. The results contribute pertinent information on the physiologic reaction in the digestive canal of these polysaccharides as they exist in food-stuffs.

# RESULTS AND DISCUSSION

Nine healthy children, ages 5 to 8 years, were observed for pre-experimental and experimental test periods from 20 to 55 days in length while living under controlled conditions in an environment permitting normal activity and conducive to normal growth and development. The details of metabolic procedure, methods and care of the children\* are described in earlier publications (16, 17). The alterations made in the daily diets of the subjects during the experimental periods are shown in Table I. It is important to note that seven of the subjects received 100 grams of apple throughout the study and the other two received 200 grams; also, that the seven children

were receiving 100 grams of banana during the pre-experimental period, the other two none. Three of the children received a diet increased by 100 grams of banana during the experimental period (Group I). Five of the children received 100 grams of banana instead of 30 grams of cereal (Groups II and III). One child (Group IV) received an addition of 100 grams of banana and other foods.

The effect of adjusting the dietary proportions of apple, banana and cereal upon the unavailable carbohydrate intake and the resultant fecal outgo (i.e. laxation rate, water content, dry weight, energy value and nitrogen content of the feces) are shown in Table II. The diets throughout the study conformed to dietetic standards and were comparable qualitatively† although each child served as his own control and received food in sufficient quantities to meet individual activity and growth needs.

†The diet was composed of the following foods which were fed in sufficient quantities to take care of body requirements for growth and activity: apple, banana, lean beef, white and whole wheat bread, butter, cabbage, carrots, cheese, eggs, gram crackers, lettuce, milk, peanut butter, potato, shredded wheat or corn flakes, tomato and orange juice, sugar and salt.

TABLE II

*Average daily intakes and disappearance of cellulose and hemicellulose in the alimentary tracts of children*

							Nitrogen				Fecal Outgo				Cellulose		Hemicellulose	
	Observation Period (days)	Initial Age (mo./ day)	Weight (kg.)	Recum- bent Length (cm.)	Energy Intake† (Cal./ kg.)	Water* Intake (gm./ kg.)	Intake† (mg./ kg.)	Reten- tion (mg./ kg.)	Laxa- tion Rate**	Wet Weight (gm./ kg.)	Dry Weight (gm./ kg.)	Energy Value† (Cal./ kg.)	Nitro- gen Con- tent† (mg./ kg.)	Intake (mg./ kg.)	Per Cent Intake Disap- pearing	Intake (mg./ kg.)	Per Cent Intake Disap- pearing	
Group I:																		
H.H., Pre- experimental	35	84/24	20.76	119.8	90	57.4	497	4	1.7	3.3	0.69	3	55	111.8	81	119.0	63	
Experimental	40	85/28	21.33	120.2	93	62.5	489	20	2.4	4.7	0.75	4	64	120.0	79	122.8	63	
F.C., Pre- experimental	35	79/5	21.60	119.4	87	57.7	478	4	1.4	3.7	0.66	3	41	107.1	78	113.1	66	
Experimental	40	80/9	22.40	120.1	88	61.0	466	18	1.8	4.7	0.75	3	50	114.3	70	117.0	60	
D.P., Pre- experimental	35	98/20	27.68	136.0	69	46.2	373	2	1.3	2.5	0.57	3	42	83.8	78	89.2	63	
Experimental	30	99/24	27.60	137.1	72	47.9	378	2	1.3	2.5	0.48	2	34	92.3	80	93.8	73	
Group II:																		
R.S., Pre- experimental	30	65/17	18.26	114.0	90	66.2	517	43	2.7	8.3	1.24	5	65	113.8	73	118.8	39	
Experimental	20	66/21	18.40	114.7	89	67.8	503	19	2.8	7.0	0.98	4	59	110.4	72	98.9	52	
+B.M., Pre- experimental	30	63/7	16.23	104.1	100	72.5	582	27	1.8	6.0	1.02	4	64	128.2	64	133.7	37	
Experimental	30	64/6	16.88	105.3	96	72.6	549	26	2.0	5.4	0.74	4	55	120.3	79	107.2	61	
J.H., Pre- experimental	30	55/22	16.84	106.9	97	73.9	561	13	2.0	4.2	0.82	4	59	123.5	91	128.5	67	
Experimental	30	56/21	16.87	107.4	97	73.5	549	10	1.7	3.6	0.67	3	52	120.4	91	107.3	71	
Group III:																		
J.M., Pre- experimental	40	75/3	20.64	116.4	85	54.5	498	24	1.0	3.8	0.61	3	47	123.5	78	121.6	70	
Experimental	45	76/17	21.58	117.4	82	56.3	464	29	1.1	3.6	0.66	3	44	115.8	79	99.8	66	
+B.F., Pre- experimental	40	69/12	18.43	110.5	95	63.2	558	20	1.8	5.8	0.80	4	60	138.3	61	136.2	61	
Experimental	50	70/12	19.28	111.4	91	66.6	520	36	1.7	4.9	0.86	4	54	129.6	65	111.7	58	
Group IV:																		
+P.W., Pre- experimental	55	75/29	20.21	116.8	80	53.6	458	—6	0.9	3.7	0.67	3	43	103.0	59	107.4	58	
Experimental	25	78/3	21.15	118.2	93	62.1	495	38	1.2	4.2	0.79	3	48	121.6	60	124.4	59	
Pre-experimental period of 330 days — Mean			20.20	116.3	87	59.6	500	13	1.5	4.5	0.77	3	52	114.2		117.9		
Experimental period of 310 days — Mean			20.71	116.8	89	63.0	490	23	1.7	4.4	0.74	3	51	117.1		109.7		

\*Total water consumption.

\*\*Number of bowel movements per day.

†Female.

†Determined by the Parr Oxygen Bomb Calorimeter method.

†Determined by the boric acid modification of the Kjeldahl method.

Banana and apple have similar nutritive characteristics which seem to reside in the carbohydrate moiety (11-13). These two fruits have the same amount of total fibrous residue but the distributions of the individual unavailable carbohydrates are different; the banana contains a preponderance of lignin while apple possesses less lignin but more cellulose and hemicellulose. Cereals vary in their content of total fiber and their composition depends upon the portion of the whole grain that is used. The decomposition or fermentation of the crude fiber in the digestive tract of man is affected by the age and make up of the plant cell membrane, the proportion of the component unavailable carbohydrates, and by the dietary mixture as a whole (10). For these reasons the bananas<sup>†</sup> were fed at the stage of ripeness at which the fruit is considered to possess maximum food value; the apples were of the same variety, and the same foods made up the basal dietary for each day.

The intakes of total fiber were greater than the physiologic roughage minimum of 90 to 100 mg. per kilogram of body weight that Cowgill and Anderson (3) considered necessary for satisfactory elimination in healthy adult men. The dietary changes for eight of the children did not alter the fiber content of the total diet more than 14 per cent, an amount less than the 25 per cent Cowgill and Anderson found necessary to effect a laxation response. The subject's daily cellulose consumption per kilogram of body weight ranged between 84 and 138 mg. and their hemicellulose intake from 89 to 136 mg.

The addition of 100 grams of banana to the diets of the three children in Group I increased their daily cellulose intakes 7.2 to 8.5 mg. (111.8 to 120.0: 107.1 to 114.3: 83.8 to 92.3) and their hemicellulose intakes 3.8 to 4.6 mg. (119.0 to 122.8: 113.1 to 117.0: 89.2 to 93.8) per kilogram of body weight. Since the total residue of banana is approximately 60 per cent lignin, 25 per cent cellulose, and 15 per cent hemicellulose (2), the lignin in the diets was augmented in greater proportion than the other unavailable carbohydrates. The caloric intakes per kilogram of body weight were raised 1 to 3 calories, the water 2 to 5 grams. In a preceding paper (18) presenting the nitrogen and mineral balances of the subjects during the study the additional 100 grams of banana daily was shown to be accompanied by increased average daily retentions or an increased per cent of intake retained for nitrogen, calcium, magnesium, sodium, potassium, phosphorus, chlorine and sulfur.

For H.H. and F.C., the increases in the intakes of banana were accompanied by an increase in laxation rate and the feces contained more water, solid material and nitrogen, indicating that the fecal material had remained in the alimentary tract for a shorter period of time. During the pre-experimental period 81 and 78 per cent of the cellulose intake was decomposed in its passage through the digestive tracts of H.H. and F.C., in contrast to 79 and 70 per cent, respectively, when the banana supplement was given. Likewise, 63 and 66 per cent of the hemicellulose intake disappeared in the digestive tract for these same children during the pre-experimental regimen whereas 63 and 60 per cent were broken down, respectively, during the experimental periods. Apparently these two children were able to utilize the cellulose and hemicellulose of

the banana better than that of the diet as a whole for in spite of the increased elimination with a greater output of unutilized intestinal products and a reduced nitrogen intake (8 and 12 mg. per kilogram of body weight, respectively) during the period when additional banana was given, there occurred simultaneously an augmented rate of nitrogen storage. The increased fiber or water intake, or both, may have been responsible for the stimulated laxation rate.

The third child in Group I (D.P.) showed no change in laxation rate or nitrogen retention, a decrease in energy value and a slight increase in water content of the feces. The subject's water and nitrogen intakes were slightly increased yet the dry weights and nitrogen contents of the feces per kilogram of body weight were reduced. This response implies an unusual ability of D.P. to break down the fibrous food substances passing through his digestive tract. During the pre-experimental period 78 and 63 per cent of the cellulose and hemicellulose intakes disappeared in transit through the alimentary canal. After the fiber intake was increased, 80 and 73 per cent, respectively, of the cellulose and hemicellulose ingested disappeared. Further support of this individual's superior ability to decompose fiber by means of a particular bacterial flora or some other factor, leaving insufficient quantities of roughage to stimulate elimination, is found in his low gastro-intestinal motility, determined in roentgenologic studies (19). This observation is in agreement with the findings of Cowgill and Sullivan (4) who observed that some patients with constipation have a greater tendency to decompose fiber in their digestive tracts than healthy men.

Each of the five children in Groups II and III were subject to the same alteration in diet during the experimental period and were receiving approximately the same quantities of fiber from either apple or banana during the pre-experimental period, although the subjects in Group II received 100 grams of each fruit daily and those in Group III received 200 grams of apple, which contains less lignin and more cellulose and hemicellulose than banana. Throughout both intervals of study the energy values of the intakes were within the range 82 to 100 calories per kilogram of body weight per day. The cellulose ranged from 110 to 138 mg. and the hemicellulose from 99 to 136 mg. per kilogram of body weight per day. Substitution of 100 grams of banana for 30 grams of cereal during the experimental period reduced the nitrogen intake of each child by an amount ranging from 12 to 38 mg. per kilogram of body weight while little change occurred in the amounts of water ingested. The cellulose and hemicellulose contents of the diets were reduced by 8.7 to 3.1 mg. and 26.5 to 19.9 mg., respectively, per kilogram of body weight during the experimental period.

In response to the diet substitution little change could be found in the laxation rates of the 5 children but the daily water and nitrogen contents of the stools were lowered for all of the subjects. Changes in nitrogen retentions, dry weights of feces and disappearance of cellulose and hemicellulose were altered by the different proportions of apple and banana in the diets of the two groups. The three children in Group II who, throughout both periods, each received 100 grams of banana per day more than J.M. or B.F. (Group

<sup>†</sup>The bananas were selected by Mr. R. E. Reiff of the Fruit Dispatch Company, Detroit.

III), all reduced their nitrogen retentions per kilogram of body weight during the experimental period. The average daily dry weights of their feces were lessened also and although only one child (B.M.) appreciably increased (15 per cent of intake) in daily disappearance of cellulose, all three children showed an increased amount of hemicellulose disappearing in the tract (4 to 24 per cent of intake). The two children in Group III received more apple than banana throughout the study. Their daily nitrogen retentions and fecal dry weights per kilogram of body weight increased during the experimental period and there was a slight change in the quantities of carbohydrates disappearing from their tracts, an increase of 1 and 4 per cent of the cellulose and a decrease of 4 and 3 per cent of the hemicellulose intakes, respectively.

P.W., whose diet was increased with foods in addition to banana during the experimental period because of increased growth demands, illustrates the significant changes that may take place in the proportion of complex carbohydrates ingested when a diet is augmented. It has been pointed out in another communication (1) that in this study of children during periods in which each subject's caloric intake and its alkaline-ash and acid-ash values per kilogram of body weight per day were practically constant, although the intake of excess base was increased during the experimental period to make it more compatible with optimal growth needs, there are other motivating factors besides quantity intake of nitrogen that affect the nitrogen retention and growth of tissue when conservative amounts of banana are added to the diet. The unavailable carbohydrates may have a protein-sparing action and the character of the fiber (i.e., the proportion of lignin to cellulose to hemicellulose) may have physiologic importance in the diet.

It is known that banana increased the lignin content of the diet (Table II) changing the quantities of both cellulose and hemicellulose fermented in the digestive tract and added some pectin (about one per cent of the fresh pulp) which seems to have unique physiologic value in stimulating more wholesome utilization and passage of intestinal contents (11-13), a more satisfactory buffer action (12, 13, 20), and effects a change in the bacterial flora of the feces (21). The tannin content of banana may also be of some significance (22). Since there are so many other dietary properties inherent in banana, consideration must be given to the food as a whole and its effect upon elimination and

gastro-intestinal motility and the utilization of the individual mineral elements (22).

## SUMMARY

The disappearance of unavailable carbohydrates from the alimentary tracts of 9 normal children, ages 5 to 8 years, was determined during pre-experimental periods of 30 to 55 consecutive days for each child and experimental periods of 20 to 50 consecutive days immediately following for each subject. The diets of the children were composed of the same foods but the quantities varied according to the size and activity of the individual. All of the children received an additional 100 grams of banana per day in the experimental regimen although the added fruit was substituted for bread and cereal in the diets of 5 subjects and one subject received the additional banana plus more potato, bread and butter in the experimental period diet.

The addition or substitution of conservative amounts of banana (one or two medium sized) did not change the caloric intake of any subject more than 4 calories per kilogram of body weight. On a unit weight basis the average intake of water was increased approximately 3 grams. While the average intake of cellulose was increased approximately 3 mg. per kilogram of body weight the average per cent of intake disappearing in the tracts increased only slightly, from 73 per cent at the beginning to 75 per cent later. The average intake of hemicellulose decreased 8 mg. per kilogram of body weight but the average per cent of intake disappearing increased from 60 to 63 per cent. The average nitrogen intake was decreased 10 mg. (500 to 490) per kilogram of body weight per day during the experimental period but during this interval the average daily nitrogen retention per kilogram of body weight increased from 13 to 23 mg. The average laxation rate increased from 1.5 to 1.7 and the average wet and dry weights of the feces dropped from 4.5 to 4.4 grams and 0.77 to 0.74 grams, respectively, per kilogram of body weight.

The variations of the individuals in disappearance of fiber from the tract are shown to be characteristic and are related to the proportions of lignin, cellulose and hemicellulose in the daily diet more closely than to total quantity intake of fiber, although the form in which the unavailable carbohydrates are ingested and other factors (vitamins, pectin, tannin, etc.) probably play an important part in determining the physiologic response to altered intake of unavailable carbohydrates.

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## Dysphagia Ascribed to Vitamin B Deficiency\*

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A NUMBER of diseases involving the esophagus, larynx, pharynx or the cardiac end of the stomach have in common a variable amount of difficulty or pain on swallowing. Functional disturbances of these organs as well as pressure upon them from without or foreign bodies within them may also produce this symptom. Furthermore, certain lesions within the central nervous system like multiple sclerosis, polio-encephalitis or bulbar palsy may cause dysphagia. Myasthenia gravis, too, may be a cause of some difficulty on swallowing. Likewise, dysphagia may be a manifestation of hysteria. Finally, deficiency states may cause dysphagia, but on the other hand, dysphagia and the accompanying limitation of food intake may produce not only loss of weight, emaciation and dehydration, but also deficiency states.

The Plummer-Vinson syndrome is apparently an iron deficiency state (1) and is characterized by a hypochromic anemia and dysphagia with or without an acidity of the stomach. The difficulty in swallowing in this condition is usually relieved by adequate iron administration. Similarly, a dysphagia caused by a Vitamin B deficiency has been described in pellagra and sprue. Six cases of dysphagia, none of which had either pellagra or sprue, were relieved by the administration of the Vitamin B group and are reported here.

### REPORT OF CASES

*Case 1.* E. G., female, 22 years old. During the last seven months the patient voluntarily restricted her diet in order to reduce her weight. She lost 40 pounds (from 160-120). She then developed an obstipation followed by severe polyneuritis involving both legs and later both forearms as well. During the past two weeks she noticed increasing difficulty on swallowing food. At first only solid food caused discomfort but gradually also liquid food became difficult to swallow. There was no regurgitation of food or vomiting. The patient was hospitalized because of dehydration, weakness and paresis of both legs. The physical examination was essentially negative and the Roentgen-ray examination of the gastro-intestinal tract showed no demonstrable pathology. No gastric analysis was done. The blood cytology and chemistry was within normal limits. Under intensive Vitamin B therapy, which consisted of intramuscular injections of liver extract and thiamin chloride and oral administration of nicotinic acid, her dysphagia disappeared within eight days and the polyneuritis cleared up in seventeen days.

*Case 2.* C. B., female, 42 years old, complained of dysphagia for seventeen years. There were also retrosternal pain, pain in the calves of both legs and general weakness. The onset of the dysphagia was gradual and the course

was intermittent but progressive. The patient restricted her diet to liquids and white bread soaked in milk or tea. The physical examination revealed an undernourished individual, weighing 111 pounds, anemic and somewhat dehydrated. There were several purpuric spots on the right thigh and left forearm. The red blood count was 3,800,000 and hemoglobin 65% (Sahli). There was free HCl in the gastric contents. Roentgen-ray examination revealed a normal esophagus. A number 56F esophageal bougie was passed without meeting obstruction or delay.

She was given liver extract intramuscularly for three months with practically complete relief. Now, a year later, the patient is taking a general diet and has no further complaints about difficulty on swallowing. Her present weight is 137 pounds, and her blood cytology is within normal limits.

*Case 3.* E. R., female, 55 years old, complained of burning pain in the epigastrium and a sensation of a lump in the lower thorax when swallowing. These symptoms persisted for six months and were aggravated by solid foods or cold liquids. She limited her diet to soft solids and milk. There was no weight loss. At no time was there any regurgitation of food or vomiting. The patient was afraid to take solid foods. Her appetite was poor. Weight was 127 pounds. Her physical examination was essentially negative except some elevation of the blood pressure. The red blood count was 4,270,000 and hemoglobin 86% (Sahli). Gastric analysis showed no free HCl even after histamine. Roentgen-ray examination showed no pathology within the esophagus. This patient was given Vitamin B Complex and Thiamin Chloride by mouth. Within three weeks the patient was able to partake of meat and other solid foods without any discomfort on swallowing. The epigastric burning, however, persisted and was only relieved when dilute hydrochloric acid was added to her medication.

*Case 4.* M. D., female, 65 years old, complained of weakness, dizziness, and dysphagia on swallowing solid food of four weeks duration. There was no regurgitation of food nor vomiting. There was no loss of weight. The physical examination was negative except a blood pressure of 160/100. The red blood count was 5,000,000 and hemoglobin 92% (Sahli). Gastric analysis revealed no free HCl even after histamine. A small diverticulum about the middle third of the esophagus was the only variation from normal demonstrated by Roentgen-rays.

The patient rapidly improved on treatment with Vitamin B Complex administered by mouth. However, four months later when she omitted her medication for several weeks there was another period of dysphagia despite an adequate diet.

*Case 5.* L. DiC., female, 24 years old, complained of retrosternal and epigastric distress of three years duration. At first the discomfort came intermittently, usually 1-2 hours after meals, but during the last two weeks it became constant. It was aggravated immediately after partaking of food. She also complained of anorexia and

\*From the Gastro-Intestinal Clinic of the Boston City Hospital, Boston, Mass.  
Submitted February 18, 1940.

nausea. She had limited her diet to soft food because of an increasing dysphagia. There was also generalized weakness and aches in the arms and legs. Numbness and tingling of fingers was another complaint of the patient. There was no loss of weight. The physical examination was entirely negative. Gastro-intestinal Roentgen-ray examination revealed no demonstrable disease. Gastric analysis showed no free HCl even after histamine. There was no anemia. Vitamin B Complex rapidly relieved the dysphagia and retrosternal and epigastric distress, but the general weakness and aches in both legs persisted.

Case 6. G. M., female, 46 years old, consulted her physician for dizziness and vertigo associated with the onset of her menopause. She was given estrogenic therapy with excellent results. Throughout this time she was on a well balanced diet obviously sufficient in Vitamin B. Seven months later she developed a sensation of a lump behind the sternum and mild dysphagia. There was some nausea, but no regurgitation or vomiting. The red blood count was 4,850,000 and hemoglobin 91% (Sahli). She was placed on thiamin chloride by mouth and was promptly relieved of her complaints. However, within three or four weeks after she discontinued her medication, there was a definite recurrence of her symptoms despite an adequate diet. Again, the administration of thiamin chloride relieved her symptoms.

### DISCUSSION

These six cases present dysphagia as the one complaint common to all, although the onset, duration, course and degree of it varied from case to case. Thus, there are cases with an acute onset and marked dysphagia like Case 1 and chronic cases with an intermittent course like Case 2. In only one instance (Case 4) was any deviation from normal observed in the esophagus. The small diverticulum, it was felt, played no part in the causation of the dysphagia. All cases were studied for organic disease, not only of the digestive tract and cardio-respiratory system, but also of the nervous system. In two instances (Cases 4 and 5) a previous diagnosis of hysterical dysphagia was made.

All six patients were females. Their ages ranged from 22 to 65. The dysphagia lasted from two weeks to seventeen years. In four cases a gastric analysis was done and in three of these an achylia was found. Wilbur (2) believes that interference with the secretion of hydrochloric acid is present in many cases of Vitamin B deficiency. In five cases other evidence of Vitamin B deficiency was noted: general weakness, neuritis, pain in the calves of the legs, anorexia, consti-

pation. In one case there was also evidence of Vitamin C deficiency.

The diagnosis of dysphagia due to Vitamin B deficiency is made by the elimination of all other causes of dysphagia, careful analysis of the patient's diet and finally by observing the results of Vitamin B administration. The ruling out of a hysterical dysphagia may present serious difficulties. As a matter of fact, in two of the reported cases this diagnosis was originally made, but the response of these cases to Vitamin B therapy, it is felt, justifies the latter diagnosis.

As a therapeutic test two cases with marked dysphagia, one due to cardio-spasm and the other due to an old polio-encephalitis were given for a prolonged period very large doses of Vitamin B without any improvement.

From this and other observations it is fair to conclude that the administration of this vitamin alleviates the dysphagia only when the condition is caused by an avitaminosis.

No attempt is made to explain the mechanism of this dysphagia. Suffice it to say, that it is usually due to a diet obviously poor in Vitamin B, but occasionally as in Case 6, it may occur despite an apparently adequate diet. One more question deserves discussion: which fraction of Vitamin B causes dysphagia? This must remain unanswered at this time and await further information. The clinical impression gained is that Vitamin B Complex is superior to either liver or thiamin chloride, both of which have been tried singly. According to Wilbur (2) dysphagia is probably not caused by lack of either Vitamin B<sub>1</sub> or nicotinic acid.

Finally, it is felt that in cases of unexplained dysphagia, Vitamin B administration is justified as a therapeutic test.

### CONCLUSION

Six cases of dysphagia caused by Vitamin B deficiency and relieved by adequate Vitamin B administration are reported. The diagnosis is made on careful analysis of the dietary habits of the patient, the absence of other causes of dysphagia and the response to adequate Vitamin B therapy. Two cases of dysphagia due to other causes used as a control did not respond favorably to Vitamin B administration.

### REFERENCES

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2. Wilbur, D. L.: The Effects of Vitamin Deficiency on the Gastro-Intestinal Tract. *Am. J. Dig. Dis.*, 6:610, Nov., 1939.

## Editorials

### THE RATIONALE OF BILE SALT THERAPY IN BILIARY TRACT DISEASE\*

ALL over the world physicians tend to give bile salts or laxatives containing bile or bile salts to patients who complain of symptoms suggesting cholecystitis or disease of the liver. The thoughtful clinician will wonder how much of this therapy is based on the ancient doctrine of "like cures like" and how much is based on scientific reasoning and observation. In those cases in which bile is not entering the duodenum it is conceivable that the giving of bile might

do some good, but if, as usually happens in cases of cholecystitis, there is plenty of bile in the bowel, what can one hope to accomplish by giving bile or bile salts?

Theoretically one can increase the secretion of bile and can perhaps thereby to some extent flush the ducts, but will this do any good? Furthermore, will the flushing of the hepatic and common ducts speed up the current of bile in and out of the gall bladder? Finally, can such a speeding up, if accomplished, have any influence on gall stones, on infection deep in the wall of the gall bladder, or on the symptoms?

In an attempt to answer some of these questions, we have performed over 200 experiments on some seventy-

\*The Rationale of Bile Salt Therapy. *Minnesota Med.*, 22:815, Dec., 1939.



five dogs provided with a long-maintained biliary fistula.

First, it may be remembered that the bile serves the body in several ways, and that actually, the bile salts have most to do with carrying out these functions. These salts are formed by the conjugation of lithocholic, desoxycholic and cholic acids with taurine and glycine. The resultant salts aid in the digestion and absorption of fats and the fat-soluble vitamins. They help to prevent the precipitation of cholesterol by keeping the fatty acids in solution. They promote the flow of bile, and by stimulating intestinal activity they have a laxative action.

The bile salts used in our work fall into three groups: First, the natural bile salts, such as are exemplified by "Bilron" and Wilson's Purified Bile Salts; second, the oxidized conjugated bile salts such as Dechacid No. 14, and third, the oxidized unconjugated bile salts or the dehydrocholates, such as Ketochol and Decholin.

The greatest stimulation of biliary flow has been obtained with Decholin and Ketochol administered orally. It now appears certain that the oxidized unconjugated salts have little if any effect upon the output of cholic acid. The oxidized conjugated bile salt Dechacid No. 14, has stimulated bile flow only slightly, and has had little if any effect upon the synthesis of cholic acid.

The natural bile salts have produced only a moderate flow of bile but they have markedly increased the output of cholic acid. When these natural bile salts were given by mouth the additional cholic acid secreted amounted to approximately 90 per cent of the cholates administered. None of the bile salts used in our work had any effect upon the output of total pigment. The cholesterol output, in all cases, was increased except when Decholin was given by mouth. Decholin decreased the output of cholesterol. This unexpected result we cannot at present explain.

The oxidized unconjugated bile salts, such as Decholin and Ketochol, are reported to be less toxic when injected intravenously than are the natural unoxidized bile salts. Daily injections of 1-2 cc. of a 20 per cent solution of Decholin are being used by some men after operations on the gall bladder and biliary tract. However, since bile salts are so readily absorbed from the intestine, there is no indication for intravenous therapy other than to obtain a "priming" effect on the liver. With oral use, the question of toxicity does not have to be so seriously considered. We have shown, during the last few months, that long-continued feedings of both the oxidized and natural bile salts have no detectable deleterious effects on the animal or on its liver.

At the present time, the therapeutic value of a preparation of bile salts is usually thought to depend on the degree to which it stimulates the flow of bile. Thus, in biliary tract disease without acute hepatitis, bile salts are administered to "flush" or "wash out" the biliary passages with a copious flow of bile of low viscosity. When such a result is desired the oxidized unconjugated bile salts, such as Decholin and Ketochol, per gram weight, are preferable, as indicated by our extended observations on the dog. In the presence of hepatitis, the effect of the various bile salts, in our opinion, is problematic. In the presence of the degree of hepatitis we have dealt with, we have not observed stimulation either of volume output or of cholic acid

production. Obviously such experiments on man or animals are very difficult, if not impossible, to control.

That these bile salts will at the same time flush out the gall bladder has not yet been ascertained. Experiments are being performed in our laboratory to determine whether bile salts have such an action. Other important points to be considered in the choice of a bile salt preparation are its cholic acid content and its effect on the cholic acid output of the liver.

When bile is not getting into the intestine, the giving of natural bile salts, such as Bilron and Wilson's Purified Bile Salts, is indicated to improve the digestion and absorptions of foods, especially fats, and also the absorption of fat-soluble vitamins. The effect of the oxidized bile salts upon digestion and absorption has not been thoroughly investigated. The available evidence indicates that they act like natural bile salts, hog's bile, or Desichol in improving the absorption of Vitamin K.

As we said at the beginning, the use of bile or bile salts in medicine can be a scientifically directed procedure only when it can be shown by laboratory tests that the liver and biliary tract of the patient are functioning abnormally in such a way that bile salt substitution or additive therapy will tend to correct the disturbance. Further, it should be noted that one cannot assume, because the fecal matter is pigmented, that the liver is putting out bile salts. The liver can produce pigmented bile which contains little if any cholic acid.

A. C. Ivy and A. L. Berman.

#### CONGRATULATIONS TO DR. FRANK LAHEY ON HIS SIXTIETH BIRTHDAY

IT is hard to believe that dynamic, hard-driving, young looking Frank Lahey is sixty, but he is and has been since the first of June. The editors and publisher of this Journal and the many members of the American Gastro-Enterological Association are happy to join with the Staff of the Lahey Clinic and Dr. Lahey's many friends all over the country in sending him congratulations and messages of friendship, admiration and affection.

Because of his outstanding work in the surgery of the digestive tract Dr. Lahey in 1932 was invited to become a member of the American Gastro-Enterological Association. He has attended the meetings regularly, always contributing something of value and always presenting his material well. Because of this ability as a teacher Dr. Lahey is today one of the most popular speakers on the medical lecture platform. He impresses everyone with his thorough grasp of his subject, the earnestness and excellence of his presentation, and the honesty with which he speaks of his failures as well as of his successes.

Our kindest greetings to you, Frank, and may you have many more years in which to enjoy life, to study and teach, and to watch and direct the growth of your splendid clinic.

W. C. A.

#### THERAPY OF CHRONIC GASTRITIS

CHRONIC atrophic gastritis is frequently found together with a deficiency state. It is well known that it most regularly occurs in pernicious anemia and idiopathic microcytic anemia due to iron deficiency. The relationship between the deficiency state and the atrophic inflammation of the gastric mucosa is still debatable. It has been assumed, especially by Faber

and Hurst, that the gastritis is the primary disease leading to a secondary deficiency state. However, recently the opinion seems to be prevalent that the deficiency state is the cause of the atrophic gastritis. The observations, made at first by Chester Jones, Benedict and Hampton, that apparent regeneration of the atrophic gastric mucosa in pernicious anemia may follow the administration of liver, seem to support the idea that atrophic gastritis is secondary to the lack of the anti-anemic factor. This assumption led to attempts to treat also cases of atrophic gastritis without a known deficiency state by substitution therapy.

The first cases in which the gastric mucosa apparently responded to such therapy were reported by Paul Chevallier and Moutier. It could hardly be expected that every case of atrophic gastritis would respond to such therapy because we know that in many cases this disease develops slowly from a superficial gastritis; and, although there might be cases of superficial gastritis due to a deficiency state also, this probably is not true for the majority of such cases. However, some observers found rather constantly good results after treatment of atrophic gastritis with liver injections or with oral administration of ventriculin. The disappearance of the subjective symptoms does not prove the value of any kind of therapy in a disease like atrophic gastritis, which has so many spontaneous remissions. Only the change of the gastroscopic picture is significant, because in severe chronic atrophic gastritis spontaneous changes of the characteristic picture are not seen.

Uniformly good results have not been obtained with substitution therapy by Kirsner, Palmer, and myself.\* In eight cases of atrophic gastritis in which frequent gastroscopic checks were possible the patients were so treated. In these cases the gastroscopic picture did not change after liver therapy. In four cases the gastric mucosa became apparently normal after the administration of liver, but in two cases the atrophy reappeared when this treatment was interrupted. Iron therapy was apparently successful in one case. Vitamin therapy was tried but no statement can as yet be made about its value. In one of the cases, showing gastroscopically a spectacular improvement, some free hydrochloric acid reappeared after liver therapy, suggesting perhaps a true regeneration of functionally active glandular structures. These results are rather encouraging. While one cannot expect at present to cure all cases of atrophic gastritis, the attempt to influence the gastric mucosa by injections of liver extract, or by iron, or perhaps even by the administration of vitamins should be made in those cases in which a definite diagnosis of extensive atrophic gastritis is established.

R. Schindler.

\*Rudolf Schindler, M.D., Joseph B. Kirsner, M.D. and Walter Lincoln Palmer, M.D.: "Atrophic Gastritis: Gastroscopic Studies on the Effects of Liver and Iron Therapy. Preliminary Report. *Arch. Int. Med.*, Vol. 15, p. 78, 1940.

## TWO NEW AND HOPEFUL SUGGESTIONS FOR THE TREATMENT OF CANCER

IN the November, 1939, number of the Proceedings of the Society for Experimental Biology and Medicine, Guyer and Claus reported some interesting and encouraging studies which were started with the idea that cancer cells are most vulnerable to the roentgen rays during the prophase and metaphase stages of nuclear division. Since colchicine arrests mitosis in

metaphase and holds it there for from fifteen to twenty-five hours, it seemed probable that the irradiation of tumors would be more effective if the animal were first to be given a dose of the drug.

Acting on this plan, Guyer and Claus treated 672 rats, some cancer-bearing and others used for controls. After the proper dosages had been worked out and the optimal interval had been found between the giving of the drug and the irradiation, the results of the combined treatment were found to be decidedly better than those of irradiation alone. Interestingly, also, it was found that the results were much better if the irradiation was given in small doses twice a week. It will be interesting to see if this technic can be used in man and if it then gives good results similar to those obtained in the rats.

Another most promising suggestion has come recently from the physicists (*Science News Letter*, January 13, 1940). They have known for some time that if neutrons are led into hydrogen, water or paraffin, they will collide with atoms until soon they have lost all their energy and have been rendered harmless to living tissues. But if one of these harmless neutrons comes near a boron atom it is sucked in. As a result the boron promptly gives off a form of radiation which will kill cancer cells. Already Dr. P. S. Kruger, working in the Radiation Laboratory of the University of California, has shown in vitro how effective this action can be in destroying sarcoma cells. Now all that is needed is the synthesis of a compound of boron which will have an affinity for cancer cells, and then large doses of radiation can be applied to these cells without hurting the normal tissues of the body.

W. C. A.

## THE ABSORPTION AND EXCRETION OF IRON BY THE INTESTINE

FOR years one of the problems that has troubled physicians has been, how is iron absorbed from the digestive tract. The great difficulty in getting a clear-cut answer arose in the fact that research workers had no dependable method of measuring immediately the absorption of iron from the intestine. All the methods were indirect and were based largely on measurements of the amount of iron excreted. Now the problem is simplified by the demonstration that iron is transported as plasma or serum iron. It occurs in the blood stream in three states: as hemoglobin iron, as "easily split-off" iron and as plasma iron. One difficulty in the past also has been the question, how much of the iron absorbed from the bowel goes out through the lymph channels.

A large amount of research work on the problem has recently been reported by Moore, Arrowsmith, Welch and Minnich in the "*Journal of Clinical Investigation*" for September, 1939. They conclude that the rate of absorption of iron from the gastro-intestinal tract can be followed directly by measuring an increase in the amount of iron in the serum. The iron does not go out in the thoracic duct lymph.

Water-soluble, highly ionized ferrous salts appeared to be absorbed equally well in the presence or absence of normal gastric acidity. The writers believe their findings suggest that the ease of ionization of ferrous salts is the important factor in determining the rate of absorption. The nature of the anion, except as it

influences the ionization, would seem to be unimportant.

In most instances the curves showing serum iron were higher following the ingestion of ferrous than of ferric salts. The addition of large amounts of either cevitic acid or sodium formaldehyde sulfoxylate caused the ferric salts to be absorbed about as well as the ferrous salts. The impression was then that iron is absorbed largely, if not entirely, in the ferrous form. No increases in serum iron were obtained following the giving of insoluble ferrous and ferric phosphate. Patients with an iron deficiency anemia frequently seemed to absorb iron better before treatment than after they had been adequately treated. Absorption seems to take place largely in the upper part of the small bowel.

It has been stated by many writers that the bowel, and particularly the large bowel, excretes iron which has been absorbed farther *orad*. Maddock and Heath in the "Archives of Internal Medicine" for March, 1939, reported on the search for iron in the mucosa of grafts of dog's colon transplanted into the abdominal wall, with the mesenteric blood supply intact. Maddock and Heath concluded that there was no evidence that iron was excreted by the colon. Occasionally some iron could be shown to be present in the mucosa, but the amount of this was not increased by the giving of iron to the dog.

Hahn, Bale, Hettig, Kamen and Whipple (J. Exper. Med., 70:443, 1939) found when they gave radioactive iron to dogs *by vein* that there was a slight excretion in the stools. There was from 0.05 to 0.4 mg. daily after the animal had received from 100 to 250 mg. of the "tagged" iron molecules. When blood was destroyed by acetylphenyl hydrazine the fecal excretion rose to from 0.1 to 1 mg. a day. Much of this probably came into the bowel by way of the bile. Normally the bile contained only 0.01 mg. or less of radioactive iron a day. Evidently, then the dog does not excrete much iron by way of the intestinal wall. W. C. A.

#### THE RECOGNITION OF ABDOMINAL PAIN DUE TO HYDRONEPHROSIS

**E**VERY gastro-enterologist faced with a patient who has a puzzling pain in the abdomen, especially pain which is not closely related to any function of the digestive tract, will want to rule out disease in the kidneys before he lets the patient go for an exploratory laparotomy.

In a recent paper by Berkman and Priestley (Minnesota Medicine, 22:217, 1939) there is a good discussion of the diagnostic problems involved. Obviously, easy cases to diagnose are those in which there has been perhaps hematuria, a mass in the region of the kidney, a pain running down the course of the ureter to the bladder and testes, or disturbances of urination. The diagnosis will be suspected also whenever a little pus and blood are found in the urine. Unfortunately this hint is often passed by because, in the case of a woman, the physician assumes that the abnormal cells came from the vagina, and in the case of a man, he assumes that they came from the prostate gland. In the most puzzling cases the disease in the kidney is found simply because the internist knew it was his duty to look for it.

Unfortunately, in some patients, an uninfected hydronephrosis will give none of the usual symptoms

of kidney disease; no tumor will be felt, the urine will be clear, and a plain roentgenogram of the kidneys, ureter and bladder will reveal no abnormality. Then the disease must be found with the help of an intravenous urogram, followed perhaps by a retrograde one.

The points that Berkman and Priestley made in their paper were that the physician may suspect hydronephrosis when the pain is dull and achy and situated on the outer side of the upper part of the abdomen. Such pain is usually not referred to the lumbar region or down toward the bladder; it is not definitely localized in the renal region but ranges over the entire upper portion of one side of the abdomen. It may be present for several hours, or for a day or two, or it may be more or less constant for several days. Patients usually wake in the morning free from pain, but after they have been up for several hours it comes. Walking or standing for a while usually aggravates it, and it is particularly bad in the late afternoon after a hard day's work. Then it may last through the evening.

Some relief can be obtained by lying down; more relief can be obtained by lying on the back than on the affected side, and most relief is likely to be obtained by lying on the unaffected side. This may be the most important point elicited during the taking of the history. Occasionally, however, a patient will obtain relief by lying on the affected side. Sometimes lying on the back with the arm on the affected side placed under the loin will give relief. Patients will often stick a small pillow under the loin on the comfortable side. Unfortunately, few patients will volunteer this information, and hence it must be drawn from them.

Commonly these patients complain of loss of appetite and some nausea. Vomiting is not frequent, but it can occur.

When the diagnosis is made, these patients must generally be treated surgically. Whenever possible the kidney should be saved. Often there is an abnormal insertion of the ureter into the pelvis or there may be a narrowing of the lumen at the ureteropelvic junction by fibrosis and thickening of the tissues in this region. There may also be compression of the ureter by anomalous vessels or fibrous bands. In occasional cases the back-pressure in the kidney pelvis seems to be produced by a reversal of peristalsis in the ureter.

Naturally, an early diagnosis is highly desirable, first, to save the patient from an unnecessary appendectomy or cholecystectomy, and second, to prevent the kidney from becoming badly dilated and largely destroyed. W. C. A.

#### AN AMERICAN BUILT GASTROSCOPE

**T**HE onset of the war brought a shortage of German built gastroscopes, and since we could not interrupt our diagnosing of chronic gastric disease and the systematic fight against gastric cancer, we had to find a possibility of manufacturing an equally good instrument in this country.

A very satisfactory instrument has now been put on the market by the Cameron Surgical Specialty Company of Chicago. In this instrument some important changes have been made as compared with the old German gastroscope. The first concerns the angle of vision. After the invention of the flexible gastro-



Age plays a big part in determining the procedure to be used. Surgery is not the treatment for young people with severe bleeding, and it seems that the prognosis for people under 50 treated by medical methods is good. The patient's chance for survival is much more limited when treated surgically. When the patient is over 50, surgery is the treatment recommended though some patients are in such poor physical condition when they enter the hospital that they cannot be operated on. Adequate operation is a long and tedious procedure. The ulcer must usually be resected to control the bleeding and sometimes another operation must then be performed to restore gastro-intestinal continuity. Often a duodenal ulcer is found on the posterior wall, removal of which requires partial gastric resection.

The field for improvement in mortality rate in massive hemorrhage of ulcer origin is in the group of patients over 50, and the benefits of surgical intervention will best be seen in this group, though it is admitted that patients in this group are poor surgical risks.

Francis D. Murphy.

SLIVE, ALEXANDER, BACHRACH, WILLIAM H. AND FOGELSON, SAMUEL J.

*The Significance of Nutrition and Gastric Acidity in the Etiology of Experimental Peptic Ulcer. S. G. O., 70:3-666, March, 1940.*

This study describes the Mann-Williamson method for experimental production of peptic ulcer in dogs and the consequent state of declining nutrition. The object of this study is to show the effect of this type of operation on gastric acidity and the parts played by operative gastric acidity and nutrition in the etiology of the ulcers after operation.

Twenty-eight dogs were used and control values were established by means of fractional gastric analyses. The operation was divided into three stages. Twenty-four dogs survived the first stage; 10 the second but only two lived long enough for the third stage and died shortly after operation. In the first stage, the distal end of the duodenum was anastomosed to the small intestine at a point 120 centimeters distal to the gastrojejunal anastomosis. This resulted in increased acidity of the gastric juice but was not due to alteration in the ability of the gastric glands to secrete acid juice.

The animals were studied for 13 weeks and after ruling out jejunal ulcer, the second stage operation was performed. A segment of the intestine between the duodeno-ileostomy and cecum was resected so only 40 centimeters of ileum remained between the two points. Though this did not alter the gastric acidity factor, the nutritional factor was reduced because the amount of intestine exposed to the action of the biliary and pancreatic juices was decreased.

The third stage was converted into the first stage by restoring the Thiry loop used in the second stage to normal. However, this did not prolong the dogs' lives.

As a result of these experiments, it was observed that the incidence of jejunal ulcer subsequent to drainage of the duodenum into the small intestine is decreased if the point of drainage is close to the site of gastrojejunal anastomosis. As a result of the operation, the gastric acidity response to an alcohol meal and histamine was higher than before though there is no relation between this and the incidence of jejunal ulcer.

Dogs which maintained nutrition and even gained weight after the high duodenal drainage operation developed ulcers when nutrition was impaired by a resection of considerable small intestine between the point of drainage and the cecum.

Francis D. Murphy.

LAHEY, FRANK H.

*A New Plan of Antecolic Duodenojejunal Anastomosis. S. G. O., 70:3-689, March, 1940.*

A very difficult problem at times is the restoration of the alimentary canal after resection of the jejunum at

such a high level that there remained such a short intra-peritoneal stump that lateral anastomosis is impossible and end-to-end is unsafe.

The new procedure described is one in which the upper jejunum is resected distal to the ligament of Treitz. The next step is mobilizing the colon after the parietal peritoneum has been cut to allow the duodenum and remaining jejunum to go anterior to the colon. Finally, a lateral anastomosis is performed antecolic. This operation has proved very satisfactory in patients with a gastrojejuno-colic fistula in whom it was necessary to resect stomach and jejunum.

COPPLESON, VICTOR M.

*Operations for Gall Stones. S. G. O., 70:3-679, March, 1940.*

There is still considerable divergence of opinion concerning technical details and indications for operation in acute cases. The gall bladder should be removed whenever possible if gall stones are present; also after cholecystostomy when it is certain the bile duct is clear.

Removal is contraindicated in those acute and subsiding cases in which there is a thick brawny infiltration with shortening of the mesentery of the cystic duct and in most cases in which, during the operation, satisfactory exposure of the region of the cystic duct cannot be obtained.

The technique of a cholecystectomy is described in detail, stressing the fact that the gall bladder should be removed from the cystic duct upward. Deciding whether or not to open the common duct is always an important question. There is no need to open the common duct when there is a single large calculus or when there are a number of calculi out of proportion to the size of the cystic duct or (2) when there is a very small and attenuated cystic duct. The common duct should be opened when a stone ion is felt along the course of the duct; (2) if jaundice was present on admission; (3) if the cystic duct is dilated; (4) if the common duct is dilated; (5) in cases of doubt.

Cholecystostomy should be reserved for those cases in which cholecystectomy is contra-indicated by general and local conditions, and should be carried out in bad risk patients or in acute cases in which adhesions and infiltration of the mesentery and cystic duct are present and in which cholecystectomy is judged to be dangerous.

Francis D. Murphy.

HOREJSI, J. AND MECL, A.

*The Metabolism of Aminoacids and the Liver Function. II. Acta Med. Scand., 99(5):435-442, 1939.*

If the liver parenchyma is normal, urea formation increases after ingestion of glycine, and its blood level rises; if the liver cell is injured, the blood urea falls. Urea synthesis is increased after glucose adm. After glycine, the blood sugar falls since glycogen storage is stimulated, but this is prevented if the liver cell has been damaged and filled with lipid bodies. There is a close association between hepatic function and the glycogen store of the liver cell.—J. F. Wilkinson (Courtesy of Biol. Abst.).

REICHERT, FREDERICK LEET.

*Chronic Duodenal Stasis; a Syndrome with Neurological Symptoms. California and West. Med., 49(1):37-42, 6 figs., 1938.*

Compression of the 3d portion of the duodenum by traction on the mesentery containing the superior mesenteric vessels is a frequent cause of chronic duodenal stasis of which the symptoms may be: lassitude, malaise, neuralgic pains, vertigo, intense headaches, abdominal discomfort, indigestion, flatulence, vomiting, constipation and "bilious attacks." Diagnosis is confirmed by roentgenological studies. Most cases respond to medical and postural treatment with high caloric, high vitamin bland food. Surgery should be resorted to as a last resort.—M. L. Isley (Courtesy of Biol. Abst.).

DAVIS, HERBERT H. AND McLAUGHLIN, CHARLES W., JR.  
*Results of Treatment in Acute Appendicitis. S. G. O., 70:3-713, March, 1940.*

This study considers the question of surgery in ruptured appendicitis cases. It covers 963 cases of acute appendicitis, 179 of which were ruptured when first seen.

Acute appendicitis is classified according to (1) non-ruptured; (2) local spreading peritonitis; (3) diffuse peritonitis; (4) abscess; (5) moribund.

Early operation of non-ruptured appendix is recommended to keep the mortality rate low. Non-ruptured appendix are seen the first day or two of the attack. Out of 784 patients, only 2 or 0.5 per cent died.

In 93 cases of early ruptured appendix seen during the first three days, there were 5 deaths, 3 due to spreading peritonitis, 1 to pulmonary embolus and 1 to secondary hemorrhage. The recommended treatment is immediate appendectomy with drainage and peritonitis usually disappears.

Diffuse peritonitis, commonly seen from the third to fifth day, is the most serious, and method of treatment is a question. The temperature rises to 102-105, tenderness and rigidity extends beyond the lower right abdominal quadrant. This study reviews 17 cases of immediate operation with a mortality rate of 60 per cent, and 14 cases of delayed operation with a mortality rate of 14 per cent. The 10 deaths after immediate operation were due to peritonitis. In delayed operation, preoperative treatment consists of absolute rest of the gastro-intestinal tract and decompression by use of gastric suction. Fluid balance is carefully maintained and sedatives given. Appendectomy is performed two or three months after recovery from peritonitis. Occasionally the appendix is destroyed by the inflammation. By careful preoperative treatment and delayed operation, it is believed the mortality rate can be decidedly lowered.

Francis D. Murphy.

WORM, MARTIN.

*Über Vorkommen und Menge von Cholin und von Cholinhaltenen Lipoiden in der Galle. Hoppe-Seyler's Zeitschr. physiol. Chem., 257(2/4):140-148, 1939.*

Very small amounts of free choline are present in the fresh bile of men, cattle and hogs. On standing under toluene or chloroform (CHCl<sub>3</sub>) at 37° or by acid hydrolysis, the free choline is increased and is derived probably from lecithin and sphingomyelin.—T. F. Gallagher (Courtesy of Biol. Abst.).

ITOH, RYOJI.

*Studies on Lipase. V. Effect of Bile Acids on the Reversible Action of Pancreatic Lipase. J. Biochem. [Tokyo] 27(2):279-281, 1938.*

The effect of bile acids on the hydrolytic and on the synthetic action of pancreatic lipase was studied. The hydrolytic as well as the synthetic reaction was augmented in proportion with the conc. of cholic, taurocholic, glycocholic, desoxycholic and dehydrocholic acid, though the desoxycholic and cholic acid in the higher conc. caused a retardation on synthesis with increasing conc.—Auth. summ. (Courtesy of Biol. Abst.).

ISHINO, NOBUYASU.

*Über das Vorkommen der Cholsäure in der Kaninchen-galle. J. Biochem. [Tokyo] 28(1):133-136, 1938.*

Small amounts of cholic acid were isolated from the rabbit bile. The isolation was unsatisfactory (only qualitatively) in the presence of large amounts of desoxycholic acid.—M. Neuhof (Courtesy of Biol. Abst.).

MORI, TANENAO UND KIMURA, TOSHIZO.

*Über die Gallensäure der Affengalle (Pithecus cyclopis). J. Biochem. [Tokyo] 27(3):381-385, 1938.*

The bile of apes (Pithecus cyclopis) contains mainly

glycocholic acid, margaric-glycocholic acid and glycochenodesoxycholic acid.—M. Neuhof (Courtesy of Biol. Abst.).

DAVIDSON, J. N. AND GARRY, R. C.

*The Absorption of Monosaccharides from the Large Intestine of the Rat Under Urethane Anaesthesia. J. Physiol., 96(2):172-175, 1939.*

The large intestine including the caecum, of rats, under urethane anaesthesia can absorb in 1½ hour only minute amounts of glucose, fructose, galactose and xylose.—T. C. Burnett (Courtesy of Biol. Abst.).

GEMMILL, W. FRANK.

*The Changing Conception of Gall Bladder Management. The Pennsylvania Med. J., Vol. 43, No. 4, pp. 477-480, Jan., 1940.*

The physiology of the gall bladder is briefly reviewed. Attention is called to the free communication between the lymphatics of the liver and those of the gall bladder, so that it is logical to believe that cholecystitis is a direct infection of the gall bladder wall from an infected liver. The duodenal drainage, when microscopy is done immediately on withdrawal of duodenal contents, compares favorably with X-ray in diagnosis of calculous cholecystitis. Non-visualization of the gall bladder by X-ray after the administration of the dye is explained. The percentages of error in comparing X-ray findings of visualized and non-visualized gall bladder with operative and postmortem findings are given. Attention is called to the liberal allowance of fat and frequent feedings, except in cases of jaundice and obstruction, instead of the old fat free diet in biliary disease. The proper preparation of the patient for operation is discussed, including the jaundiced patient. Emergency gall bladder operations are discouraged except in those rare fulminating types of gall bladder disease. Cyclopropane is the general anesthesia of choice. The post-operative treatment is discussed. The gall bladder requiring medical treatment is distinctly separated from that requiring surgical intervention. The author points out that the results of operation on non-calculous cholecystitis are unsatisfactory and he gives a final admonition that no gall bladder should be removed without definite clinical and laboratory evidence of disease.

John De Carlo and B. B. Vincent Lyon.

ELIASON, ELDRIDGE L. AND JOHNSON, JULIAN.

*The Surgical Aspects of Obstructive Jaundice. The Pennsylvania Med. J., Vol. 43, No. 4, pp. 452-456, Jan., 1940.*

The history of surgery in jaundiced patients is briefly mentioned.

The authors state that the preoperative diagnosis of the type of obstruction producing the jaundice is largely a matter of academic interest, and laparotomy is advised even in suspected cases of carcinoma of the head of the pancreas without metastasis, for fear that there may be a silent stone in the common duct.

The preoperative treatment is the same no matter what the cause of the obstruction. The patient is fed a high protein (30%) and carbohydrate (70%) diet with little or no fat. Vitamin K and bile salts are administered if prothrombin is low. Local anesthesia reinforced by cyclopropane, if necessary, and spinal anesthesia are the anesthetics of choice. Operative treatments for the various causes of obstruction are thoroughly, concisely and sensibly discussed. The postoperative treatment consists in the continuation of the preoperative care, the attention to the wound and biliary fistula if established, and in severely jaundiced patients, the administration of small transfusions of fresh blood every 8 hours for 2 or 3 days. If the patient is losing a lot of bile through the fistula it is re-fed by stomach tube, or lyophilized human bile from other patients, or lyophilized pigs' bile is fed if patient's

own bile is difficult to collect, or human bile is unobtainable.

Summarizing this article, the authors report a series of patients operated upon between 1922 and 1938, all of whom had associated obstructive jaundice. These cases consisted of 137 patients with stones in the extrahepatic ducts, 16 of whom died in the hospital and 9 others had recurrent jaundice. Of the 54 patients with suspected carcinoma of the pancreas, 19 died in the hospital; 10 are living and 4 are apparently well. 6 patients with pancreatitis, all of whom recovered. Of 24 patients with stricture of the bile ducts, 2 died in hospital and 6 others had recurrent jaundice. 7 patients with metastatic carcinoma, all died in the hospital. 2 patients had carcinoma of hepatic ducts and died in hospital. 13 patients had liver abscess and cysts and 7 died in the hospital. 6 patients had subhepatic abscess, one died in hospital and the remainder recovered.

In the opinion of the abstractors this article is a distinct contribution to the literature and should be read in full.

John De Carlo and B. B. Vincent Lyon.

JONES, CLEMENT R.

*Liquid Colloidal Aluminum Hydroxide in the Treatment of Peptic Ulcer. The Pennsylvania Med. J., Vol. 43, No. 4, pp. 468-472, Jan., 1940.*

The author gives the physical and chemical properties of liquid colloidal aluminum hydroxide. The neutralization of the acid is due to adsorption rather than chemical combination and 90% of the acid that will be taken up by any volume of the drug is adsorbed in the first 20 or 30 minutes. The advantages of treatment with colloidal aluminum hydroxide are: non toxicity; non absorbability; high acid combining power; and its inability to produce alkalosis. Furthermore its astringent effect, in the opinion of the author, may account for its beneficial action in peptic ulcer completed by hemorrhage.

Of the 43 patients treated by the author, all were in the low economic level and had difficulty in securing proper diet and sufficient rest. Nevertheless, all 43 were relieved of ulcer symptoms within an average period of slightly less than four days. 24 patients were under observation for 2 years or more. Of the 24 patients examined by Roentgen ray, 18 showed no radiologic evidence of ulcer; 1 continued to show an ulcer still active after 30 days; 1 a scar deformity; 3 a probable scar deformity; and 1 showed improvement in 30 days.

John De Carlo and B. B. Vincent Lyon.

SCHMIDT, CARL L. A., ALLEN, FRANK WORTHINGTON AND TARVER, HAROLD.

*A Theory of Protein Metabolism: The Transformation of Proteins. Science, Vol. 91, p. 18, Jan. 5, 1940.*

The authors state that the current view of protein catabolism is that proteins are hydrolyzed to their constituent amino acids, and these, in turn, are deaminized and the carbon-containing residues are then oxidized or converted into other substances. They believe that this is not the only possible way whereby proteins may be catabolized. Also while they believe that the animal organism synthesizes tissue proteins from the amino acids that enter the circulation, they are also of the belief that synthesis of proteins can take place in the body by the transformation of existing proteins into others without first being broken down to amino acids.

They point out that the chemical changes that take place in protein molecules during denaturation are indicative that transformation of one protein into another takes place without the intervening stage of amino acids.

The point that they stress is that it may be quite possible that some transformation or breakdown of the free groups in proteins occurs before hydrolysis of the peptide linkages. By such changes one type of protein may be transformed into another. From a thermodynamic viewpoint such a reaction is probably more efficient than one

that requires hydrolysis to amino acids and resynthesis from the selected amino acids.

They visualize that in protein anabolism and catabolism not only free amino acids are concerned in the reactions, but also peptides and proteins. They admit that experimental evidence in support of the latter concept is still meager.

Harry Shay.

ELMAN, ROBERT.

*Acute Hypoproteinemia Following a Single Severe Hemorrhage in the Fasting Dog. The Am. J. of Physiology, Vol. 128, pp. 332-337, Jan. 1, 1940.*

Elman found that an acute hypoproteinemia averaging a drop of 1.4 grams per cent in the concentration of serum protein and 0.63 gram per cent in the serum albumin was produced in fasting dogs within one hour after an arterial bleeding amounting to 3.5 per cent of the body weight, with immediate replacement of the same volume of Ringer's solution. The fall in serum protein and serum albumin averaged 22 and 20 per cent respectively of the pre-hemorrhage level.

The hypoproteinemia thus produced did not change significantly for 6 hours and perhaps longer; there was some evidence, however, of an increase in total circulating serum protein during this period.

These findings indicate that there is no rapid mechanism for the restoration of the concentration of serum protein or serum albumin lost by hemorrhage in the fasting dog, and the author emphasizes the importance of inducing such a restoration therapeutically in patients suffering severe blood loss.

Harry Shay.

LOEW, E. R., GRAY, J. S. AND IVY, A. C.

*The Effect of Acid Stimulation of the Duodenum Upon Experimental Hyper-Glycemia and Utilization of Glucose. The Am. J. of Physiology, pp. 298-308, Jan. 1, 1940.*

In 108 experiments from 62 dogs these authors failed to obtain evidence that acid stimulation of the duodenum enhances the utilization of intravenous glucose or reduced the hyperglycemia produced by the absorption of glucose, injection of adrenalin, or the removal of the pancreas.

Because of their failure to demonstrate that acid stimulation of the duodenum influences either the normal or elevated blood sugar level, they question the physiological basis which has been used to support the concept that a hormone which aids in the control of carbohydrate metabolism is liberated by the duodenal mucosa in response to stimulation.

Harry Shay.

ANDRUS, WILLIAM DEW., LORD, JERE W., JR. AND KAUFER, JOSEPH T.

*Studies on the Fate of Plasma Prothrombin. Scierrec, Vol. 91, p. 48, Jan. 12, 1940.*

The authors point out that in published studies on the metabolism of plasma protein attention has been directed only to its site of formation and none to its site of destruction. That plasma prothrombin is being continuously destroyed in, or lost from, the circulating blood they indicate from total hepatectomy studies in the dog. The characteristic curve of plasma prothrombin after total hepatectomy shows a rapid fall to 50 per cent of the pre-operative level three hours after operation, and a more gradual fall to approximately 5 per cent of normal by the fourteenth hour post-operatively. This fall is in no way altered when massive doses of Vitamin K and bile salts are injected into the small intestine at the time of operation.

From such experiments they conclude that the liver is the sole site of formation of plasma prothrombin, that the liver forms this substance continuously, and that plasma prothrombin disappears rapidly and continuously from the circulating blood. In dogs under proper anesthesia they collected samples of blood from the afferent and efferent



vessels of the head, lung, liver, spleen, intestine, kidney, and hind limbs. Samples from the right and left ventricles of the heart were used to test the values of plasma prothrombin in the blood before and after passing through the pulmonary circuit.

From these experiments the plasma prothrombin levels in the samples of blood before and after passing through the lungs showed the only consistent and significant differences. The average loss of prothrombin in passage through the lungs was 10.6 per cent in 17 animals that showed a difference in levels.

They considered two mechanisms theoretically possible to explain this loss: first, oxygenation of the blood and second, a specific tissue substance. They ruled out the former by obtaining no change in plasma prothrombin content by bubbling of oxygen through the blood, also by the fact that blood circulating through an atelectatic lung loses an amount of plasma prothrombin comparable to that lost in passage through a normally aerated lung. To support the second explanation they advanced the evidence that Howell and Donahue have shown that blood platelets are formed in capillaries of the lung and are being discharged continuously into the blood stream. The platelets as they undergo disintegration, initiate the first stage of the clotting process by releasing thromboplastin, which, the presence of calcium, changes prothrombin to thrombin.

Harry Shay.

FAXON, HENRY H.

*Subphrenic Abscess. New Eng. J. Med., Vol. 222, No. 8, pp. 289-297, Feb. 22, 1940.*

The author reports 175 cases studied during the years 1900 and 1938. After a review of the anatomy, which is apparently not well defined in the minds of numerous surgeons, the article discusses the subject under the following headings:

#### AGE INCIDENCE AND SEX DISTRIBUTION

The youngest patient was three years and the oldest was seventy-six. Sixty-one per cent of the cases were men.

#### ETIOLOGY

The vast majority of subphrenic abscesses originate from an extension of intraperitoneal sepsis. This occurs along the lateral gutter due to the negative pressure under the diaphragm fluctuating with respiration. The appendix, stomach and duodenum, liver and bile passages are the commonest sources of abscess formation in that order.

#### DIAGNOSIS

The presence of a persistent unexplained fever associated with a history of recent intraperitoneal sepsis should make one suspicious of abscess. The presence of tenderness over the twelfth rib or anterior costal margin; the clinical findings of a high, fixed diaphragm on the affected side together with manifestations of diaphragmatic irritation such as pain referred to the shoulder or neck, hiccoughs and discomfort on deep respiration, and X-ray confirmation as to the position and excursion of the diaphragm make the diagnosis.

#### LOCALIZATION OF THE ABSCESS

Eighty-seven per cent of the cases occurred on the right side. In order to determine the exact localization before operation the following points should be evaluated:

1. Localization of the point of maximum tenderness.
2. X-ray findings.
3. A consideration of the original septic process.
4. Aspiration of pus from a suspected area. [This the author, however, condemns unless it is done at operation].

#### TREATMENT

The retroperitoneal type of operation is advanced as the procedure of choice on the basis of theoretical and statistical evidence. The mortality rate in a series of 111 cases with various operations was 37 per cent. In separating the groups according to the type of operation, the

mortality rate in the transperitoneal approach was 55 per cent. In the transpleural approach it was 41 per cent. In the retroperitoneal operation it was 27 per cent.

Henry H. Lerner.

FENZ, EGON.

*Über die Anazidität der Diabetiker. Wiener Arch. inn. Med., 32(6):289-194, 1938.*

Tests of gastric secretion in 116 unselected diabetics showed that 56.3 per cent were anacid, 16.5 per cent normal or hyperacid. Those who had received insulin were less frequently anacid. 44 of the patients suffered from diabetic diarrhea. About  $\frac{3}{4}$  of the diarrhea cases were anacid.—E. Mendelson (Courtesy of Biol. Abst.).

IVANCEVIC, I. ET KADRKA, S.

*Action de la Asponine sur la Muqueuse Gastrique. Arch. Internat. Pharmacodyn. et Ther., 62(2):202-210, 2 figs., 1939.*

Turgescence produced by saponin on the gastric mucosa is transient, and results in augmentation of normal function. Mucus flow is greatly increased, and the volume of liquid secretion is moderately increased. Comparisons are made with effects of gentian and proteins.—G. A. E. (Courtesy of Biol. Abst.).

KANATAKE, YOSIMASA.

*The Experimental Production of Gastric Ulcer by Aliphatic Amines. J. Biochem. [Tokyo] 27(3):405-413, 5 figs., 1938.*

Aliphatic amines, such as methylamine, ethylamine, propylamine and isobutylamine in concs. above 1/15 M produced acute gastric erosion or ulcer when applied subcut. On inj. of moderate doses of amine the gastric acidity increased. The autolysis of gastric mucosa was increased by the presence of amine. When the liver was intoxicated by chloroform or P, the amine ulcer developed more seriously.—(Courtesy of Biol. Abst.).

LYALL, ALEXANDER AND NICOL, BRUCE M.

*The Gastric Secretions in Experimental Hypochloreaemia and Alkalosis Have Been Produced in Two Subjects with Gastric Hypersecretion by Continuous Removal of the Gastric Contents. J. Physiol., 96(1), 1939.*

Observations were made on the character of the gastric secretions under control conditions and during hypochloreaemia and alkalosis. No significant change occurred in the composition of the gastric juice as a result of these alterations in blood chemistry. The total volume of gastric juice was diminished.—T. C. Burnett (Courtesy of Biol. Abst.).

YOUMANS, JOHN B.

*The Influence of Vitamin Deficiencies on Other Diseases. Annals of Int. Med., XIII, Dec., 1939.*

Commenting on the prevalent practice of administration of large doses of vitamins in various disease conditions, the author offers a threefold explanation for the practice. First, the belief that the vitamin deficiency may be related as a causative factor to the disease under observation; second, that the disease may either cause or precipitate a deficiency; and third, that the pre-existing deficiency or one developing during the course of the illness will have an unfavorable effect on the course of the disease under observation. He recognizes that there are quite a number of diseases which may produce vitamin deficiency states, especially in mild or subclinical forms, but calls attention to studies done recently that appear to have failed to show that vitamin lack is responsible for many diseases except such as may be classed as gross deficiency, such as scurvy, rickets, etc., and analysis of the literature containing reports of studies on the influence of vitamin deficiencies on disease in general shows that the majority of them are



only attempts to establish an etiologic relation between a given vitamin and the disease under observation or on observations of the effect of treatment on the deficiency alone or inadequately controlled studies of the influence of such vitamin deficiencies. The lack of serious effort to demonstrate the existence of a deficiency before vitamin administration is apparent in some of the reports, while in others such experiments as were done were in effect tests of the pharmacological action of a vitamin unrelated to its function as a necessary food factor. The lack of suitable clinical methods for discovering the existence of many of the milder deficiencies of vitamins is emphasized.

After these general statements the author then reviews what he thinks constitutes the present knowledge of the influence of vitamin deficiency on disease. Most of the studies reviewed deal with Vitamin D deficiency, partly because, perhaps, of fairly satisfactory methods for determining this type of deficiency. It seems that Vitamin C deficiency in pulmonary tuberculosis parallels the severity of the disease and that improvement to some extent, at least, resulted from the relief of that deficiency. In some of the reports it appeared that a significant decrease in sedimentation rate followed Vitamin C administration, while in controlled cases no alteration in the sedimentation rate was observed. Some of the reports reviewed covered observations on red cell counts, hemoglobin, lymphocytes, monocyte-lymphocyte ratio, neutrophile-lymphocyte ratio, serum proteins, sedimentation rate, blood fibrinogen and the Schilling index, covering three, six and nine month intervals. While improvement was noted in these groups as measured by these tests, the rather peculiar observation was noted that at the end of nine months some of the advantages of Vitamin C treatment were lost. Observations on diphtheria groups in children that were on inadequate supplies of Vitamin C showed reduction of hemorrhagic manifestations when adequate amounts of the vitamin were given, but no other aspects of the disease appeared to be influenced. The literature on whooping cough as affected by liberal doses of Vitamin C appeared a bit contradictory. While improvement was noted in groups with rheumatic fever on adequate vitamin intake as compared with controlled groups, the author found but little in the literature that seemed to connect hypovitaminosis C and pneumonia. The characteristic lack of fibrous tissue formation in Vitamin C deficiency was emphasized in some of the surgical reports in which tardy healing and not infrequently rupture were observed as a consequence of C deficiency.

Despite the high incidence and severity of infections, particularly in the respiratory system, in patients presenting severe manifestations of Vitamin A deficiency and the rather widely accepted belief that Vitamin A is anti-infective, the author found no significant study of the effect of mild deficiency on the course of respiratory diseases or infections. In most of the reports reviewed failure to establish the presence of the deficiency was noted; in many the existence of such deficiency was merely assumed. In a few of the groups studied good control was noted. Studies of selected groups of students demonstrated a shorter duration of a common cold on those receiving additional Vitamin A than obtained in the control groups.

In reviewing the literature on Vitamin B<sub>1</sub> deficiency in relation to diseases of the cardiovascular system, it is concluded that the evidence was lacking that B<sub>1</sub> deficiency was productive of heart disease in the absence of other causes. Such deficiency frequently complicates a pre-existing heart disease and may at times account for some of the cardiovascular crises, but little was found in the review that established the effect of mild B<sub>1</sub> deficiencies on other forms of heart disease. The literature on the relation of B<sub>1</sub> to carbohydrate metabolism was reviewed. Some of the studies appeared to establish an increase in carbohydrate utilization, as shown by low blood sugars, the disappearance of sugar from the urine and, in some instances, a diminished need for insulin. The failure of authors to

establish an actual B<sub>1</sub> deficiency in studies relating to carbohydrate metabolism was commented on, as was found to be true with relation to other disease conditions.

After his fairly extensive review of the literature, the author concludes that there is little reliable scientific evidence of the effect of vitamin deficiencies on disease and but little justification on these grounds, therefore, for the rather widespread use of vitamins as therapeutic agents in a large number of diseases. Recognizing that while there is good reason to believe that vitamin deficiencies occur as complications of many diseases and unfavorably modify their course and outcome, yet there seems good reason to believe that with few exceptions the influence of vitamin deficiencies must be considered to be such as would be reasonably expected of poor nutrition generally without reference to specific and demonstrated effects. As methods for determining the existence of specific deficiencies of low grade manifestation are developed a much greater opportunity for critical clinical research will be opened up, and he concludes that only on the basis of such research with patients can the effect of these deficiencies and the value of treatment with specific substances be determined on human subjects.

Virgil E. Simpson, Louisville, Ky.

TURELL, R., BUDA, A. M. AND MARINO, A. W. M.

*Treatment of Pruritus Ani by Tattooing with Mercury Sulfide.* Arch. Dermat. and Syph., 41:521, March, 1940.

The authors briefly reviewed the causes of pruritus ani. They feel that the services of a team consisting of a proctologist, an internist, a dermatologist, a urologist and a gynecologist are at times necessary for the proper investigation of the rare cases of so-called essential pruritus ani. They also believe that concomitant anorectal lesions regardless of their etiologic importance in pruritus should be eliminated in all cases of pruritus ani. This policy is equally applicable to dermatologic lesions and systemic disease.

This paper is based on the study of 22 patients who had had intractable pruritus ani for many years, which was refractory to the established forms of treatment, but which responded satisfactorily to tattooing with mercury sulfide. In one case a recurrence of mild pruritus took place after 14 weeks, which disappeared spontaneously.

The armamentarium consists of an electric tattooing machine with needle handles containing 6 to 20 needles in a single row, and protruding 2 to 3 mm. A technical knowledge of the component parts of the machine such as the terminals, the switchboard, the foot switch, and the rheostat is essential. The machine and needles should be sterilized by formaldehyde vapor. A paste of mercury sulfide is used. Infiltration anesthesia with 0.5 to 1 per cent procaine hydrochloride solution is preferred. In order to evaluate the results of this form of therapy, other types of anesthesia, particularly the oil soluble anesthetics which alone are frequently employed for the relief of pruritus ani were omitted.

Considerable practice is required to master the technic. The handle of the machine should be held at an acute angle to the skin, and is advanced slowly with an even stroke. The skin should be held taut to facilitate the penetration of the needles and the mercury sulfide into the corium. At times, it is impossible to avoid missing small areas. These can be dealt with at a subsequent time, if necessary.

The untoward effects included one case of total hematuria and transient albuminuria which occurred 5 days after tattooing (this patient recovered completely); two cases of transient scaly dermatitis in the tattooed areas, and five instances of parasthesias. The latter developed within two weeks after tattooing and disappeared spontaneously within a month.

The modus operandi of this form is still unexplained. Control studies showed that the mechanical trauma alone, as produced by the tattooing machine without the use of

mercury sulfide was ineffectual in controlling pruritus and permanently.

The authors concluded that this form of therapy is satisfactory in the treatment of intractable pruritus and which fails to respond to other established procedures. They felt that the old and established modes of therapy should not be discarded until the rationale and the safety of this newer procedure are established.

Robert Turell.

DUFF, G. LYMAN.

*The Clinical and Pathological Features of Carcinoma of the Body and Tail of the Pancreas.* Bull. Johns Hopkins Hosp., 65(1):69-98, 2 pl., 1939.

16 unselected cases of primary carcinoma of the body or tail of the pancreas with adequate clinical and autopsy records are analyzed from both the clinical and pathological points of view with the object of calling attention to the tendency of cancer of the pancreas originating in the body or tail to spread in such a way as to produce clinical signs and symptoms not hitherto recognized as common. Ascites occurred in 10 of the 16 cases and hematemesis in 8 cases. Occult or gross blood was observed in the stools in 6 cases. The spleen was palpably enlarged in 4 cases and the liver in 11 cases. Slight jaundice appeared terminally in 8 cases. An account of the pathological features of carcinoma of the pancreas in general was followed by a description of the various modes and directions of spread of cancer of the body and tail of the pancreas based upon the autopsy findings in the 16 cases studied. Comparison with the autopsy findings in 16 consecutive cases of carcinoma of the head of the pancreas showed that primary cancer of the body or tail of the pancreas tended to spread much more widely and massively than carcinoma originating in the head. An adequate explanation of this tendency was afforded by a consideration of the anatomical position and relations of the body and tail as contrasted with the head of the pancreas. Direct extension of carcinoma of the body or tail of the pancreas frequently led to widespread involvement of the peritoneum and sometimes to invasion of the stomach or intestines. The abdominal lymph nodes were often massively involved. Invasion of the splenic vein with the consequent occurrence of massive metastasis to the liver might be followed by occlusion of the splenic vein, obstruction of large intrahepatic branches of the portal vein or even occlusion of the portal vein itself. These pathological developments in carcinoma of the body or tail of the pancreas were responsible for the appearance of the various clinical signs and symptoms already mentioned. Brief comment was made upon the production of each of these.—From auth. summ. (Courtesy of Biol. Abst.).

DAVISON, T. C. AND RUDDER, FRED F.

*"Factors Influencing the Mortality of Perforated Peptic Ulcer."* Southern Surgeon, 9:75-86, Feb., 1940.

A review of 155 cases showed a mortality of 28 per cent which seems entirely too high for a disease relatively easy to diagnose and treat. Factors contributing to a high mortality are delay in operation beyond six hours, age beyond 50, location high on the lesser curvature, prolonged time of operation, radical operative procedures and irritating anesthetics.

The disease is essentially that of males, the vast majority of cases occur in the third, fourth and fifth decades of life. There is often an ulcer history, the presenting symptom is the sudden onset of severe abdominal pain, the outstanding sign is a rigid abdomen, and X-ray examination may show a high pneumoperitoneum.

If preoperative shock is present it should be combatted before operation is attempted. In every instance operate as early as possible. The simplest procedure is usually the best and should consist of suturing the perforation and reinforcing the suture line with omentum. While the use of drains is debatable it seems best to use them in cases

more than six hours old. Gas with local novocain infiltration is the anesthetic of choice since spinal anesthesia as well as ether increase chest complications which are dangerous not only of their own accord but also because they lower the patients' general vitality and decrease his resistance to peritonitis.

Better cooperation especially towards early operation is urged as a measure to reduce the present high mortality.  
J. Duffy Hancock.

JACKSON, ARNOLD S.

*"Surgery of the Biliary Tract."* Southern Med. J., 33:177-181, Feb., 1940.

The policy of the Jackson Clinic is to deal conservatively with cases of acute cholecystitis allowing several days for the fever, toxemia and blood count to subside and dehydration to be relieved. Chill, increase in temperature and elevation of white count suggesting possible gangrene or empyema are indications for earlier operation. Cholecystectomy is the procedure of choice. However in the elderly, the debilitated and the deeply jaundiced, the risk of removal may be prohibitive and only cholecystostomy can be considered. Drainage after cholecystectomy is debatable. While routine exploration of the common duct will reveal many stones otherwise overlooked the best policy seems to be to reserve that procedure for those cases presenting definite indications such as: a history of jaundice, a palpable stone, a small contracted gall bladder full of stones, hydrops, or enlargement of the common duct. A common duct drain will be needed for a variable length of time usually three or four weeks.

Spinal anesthesia has caused a decrease in mortality and incidence of post-operative pneumonia, embolism, and phlebitis. Vitamin K has been most effective in preventing hemorrhage in cases of obstructive jaundice. A new oxalic acid coagulant offers great promise. Post-operative measures found satisfactory are duodenal suction, deep breathing exercises, chewing gum to prevent parotitis, frequent changes of position and leeches if phlebitis develops.

Unsatisfactory late results are too frequent but are largely due to too long delayed surgery. If the liver is allowed to become badly diseased before operation the surgeon should not be blamed for the resulting flatulence and indigestion.  
J. Duffy Hancock.

JONES, THOMAS E.

*Benign Stricture of the Intestine Due to Irradiation.* Surg. Clinics of N. A., Vol. 19, pp. 1185-1194, Oct., 1939.

Jones discusses a very important factor of disturbances of the intestine due to irradiation. Of his 15 cases, 13 occurred in the large intestine and 2 in the small intestine. Of the 3 cases described in detail, one is of stricture in the sigmoid. The radiation therapy took place 1½ years before the intestinal symptoms appeared. The complaints were those of generalized cramping pain in the abdomen, which had increased in severity and were associated with some nausea and emesis. It was necessary to resect the stricture in the sigmoid. Microscopic examination of a longitudinal section of the intestinal wall showed a narrow zone of quite marked thickening with extensive destruction of the muscular tissue and replacement by fibrous tissue at this point. Besides, there was considerable hyaline degeneration in the mesenteric vessels. The mucosal epithelium was absent, its place being taken by a small ulcer at the base of which a rather cellular granulation tissue was found.

Another case showed almost complete obstruction in the small intestine, three feet from the ileocecal valve. In this case the radium and roentgen irradiation were administered 8 years previous to the finding of the obstruction. The microscopic examination was similar to that of the first case and showed some thickening and dense fibrosis

of the serosal coat in which there were large numbers of greatly thickened arteries, showing varying degrees of obliterative endarteritis. The mucosa was somewhat atrophic and contained very little lymphoid tissue. There was considerable diffuse increase of fibrous tissue in the muscular coat, and fibrosis of the sub-mucosa.

In a third case the lesion appeared about 2 years after irradiation. The complaints were of increasing constipation and cramp-like abdominal pains. There was a narrowing and irregularity about 1 inch in length, involving the distal end of the sigmoid. There were no ulcerations present.

Jones believes that the damage in the intestines is due to the fact that the intestines were caught by the radium. He therefore suggests to stimulate peristalsis by pitressin every four hours while the radium is in place, or just previous to roentgen treatment, in order to keep the intestines moving and thus preclude extensive irradiation of any one loop.

Franz J. Lust.

#### BACHMAN, ARNOLD L.

*Calcifications in the Splenic Region. Am. J. of Roent. and Radium Therapy, Vol. XLI, No. 6, pp. 931-949, June, 1939.*

Bachman gives the following grouping for calcifications in the splenic area seen in the roentgenological examination:

- I. Splenic
  - A. Small, usually multiple shadows
    1. Phleboliths
    2. Tuberculosis
    3. Parasitic (Pentastoma)
    4. Calcifications of undetermined origin
  - B. Large, usually single shadows
    1. Perisplenitis
    2. Infarcts
    3. Hematomata
    4. Abscesses
    5. Cysts
      - a. Echinococcus
      - b. Non-parasitic
  - C. Miscellaneous
    1. General increased density of spleen
    2. Iron and calcium incrustated spleen
- II. Splenic vessels
  - A. Artery
  - B. Vein
- III. Extrasplenic
  - A. Concretions in other organs
    1. Adrenal
    2. Pancreas
    3. Retroperitoneal tissues
  - B. Miscellaneous
 

Costal cartilages, nodules in the lung and pleura, calcified trichina and cysticercus cysts, calcified glands, renal artery, concretions in the upper gastro-intestinal tract, lesions in the skin.

Bachman stresses the importance of the different densities of the spleen in portal and splenic vein thrombosis, calcified infarct of the spleen, myelogenous leukemic splenomegaly. Besides it is important to remember that we find calcifications in different types of carcinoma arising from the adrenals and the pancreas.

Franz J. Lust.

#### TURELL, R.

*The Relationship of Bacillary Dysentery Infections to Chronic Intermittent Diarrheas. Rev. Gastroentero., 7:14, Jan.-Feb., 1940.*

It was pointed-out that there exists no unanimity of opinion as to the criteria of an unequivocal diagnosis of diarrhea. A review of the important studies by Lockhart-Mummery, Dudgeon, Hurst, Thorlakson, Silverman and

others shows that an antecedent bacillary dysentery has a definite relationship to chronic ulcerative colitis.

The interpretation of the bacteriologic studies requires a knowledge of the technical difficulties and the biologic behavior of the dysentery organism. A high incidence of the dysentery bacterium is usually recovered during the first week of the disease. The acute phase may terminate the primary disease. The persistence of organisms in the chronic form of dysentery or carrier is a rarity. Furthermore, reliance should not be placed on the results of one examination. Also the intermittency of excretion of the Flexner bacillus is an important consideration as these organisms may be present in abundance for one or two days in succession and absent for 4 to 5 weeks, the end of that time they reappear.

Proctosigmoidoscopic studies of various authorities have established no difference between the picture of chronic ulcerative colitis and that of the chronic forms of bacillary dysentery. The lesions found at postmortem examination are also indistinguishable from one another.

Serum agglutination tests are still in a state of flux. Some authorities consider positive serum agglutination tests as representing present or antecedent bacillary dysentery infections. Desrenleau "considered the level of agglutination titres in the 'normal' population to indicate, in a general way, the level of endemic incidence of dysentery infection in the community. Some conception of the endemic incidence of dysentery should be revealed by consideration both of the infant mortality rate from diarrhea, and of the level of agglutination titres."

The clinician sees a large group of cases of recurring diarrhea where the agglutination tests are persistently positive in high dilution but where competent bacteriologic studies of colonic mucosal scrapings, crypt aspirations, and dejecta fail to reveal the dysentery organism. At times proctosigmoidoscopic studies show almost a normal appearing mucosa. It is felt that serum agglutination tests in high titres are of diagnostic importance because they point to a suspicious dysentery origin.

The atypical and chronic forms of bacillary dysentery is a serious public health problem. In occurrence and morbidity it outranks typhoid fever. Yet the epidemiologic surveys are very complete for typhoid fever and inadequate for bacillary dysentery.

An epidemiologic survey of bacillary dysentery should include a preliminary stool culture and a study of the agglutinins of the blood serum. In 10 to 14 days, another specimen of blood serum should be submitted for agglutination tests. A rising titre should be considered as suggestive diagnostic evidence of bacillary dysentery, as should a preliminary negative and subsequent positive tests. Additional specimens of blood collected at weekly intervals for a month, may be desirable. Cultural studies of the material obtained from the base of the ulcer, mucosal scrapings, and Lieberkuhn gland aspirations should be made as they yield a higher percentage of positive results than do similiary studies of dejecta.—Author.

#### JENKINSON, E. L. AND WASKOW, W. L.

*Polyps of the Large Bowel. Radiology, 34:489, April, 1940.*

The authors utilized the following routine procedure for the roentgenologic examination of the colon: "A light evening meal is given the day before and this is followed by two ounces of castor oil. No food is given after the castor oil, but water is permissible. The following morning, breakfast is withheld, and the patient is given a two quart tap water enema, lying on his back, and gently rolled from side to side. The patient is then given ample time to expel the enema. A light barium buttermilk water solution is then slowly injected. The head of the column is carefully watched to denote any change from a normal convex to a suspicious concave border. This is an important sign but lasts only momentarily. A small intraluminal defect is

soon inundated by the advancing column of barium. This area is then carefully palpated, pressure being applied first with the examining hand to delineate the lesion. Then by means of a balsa-wood paddle, an even pressure can be applied over the area, and, at the same time, this area of bowel under pressure can be clearly visualized on the fluoroscopic screen. Any small filling defect is then clearly outlined. With the pressure intact, a spot film is taken, since routine roentgenograms taken of a barium filled bowel are not diagnostic."

The authors discuss briefly seven of their personal cases where polyps in the descending or sigmoid colon were demonstrated by the foregoing technic.—Robert Turell.

RENSHAW, J. F.

"Role of Gastroscopy in the Diagnosis of Gastric Diseases." *Medical Clinics of North America*, 24:493, No. 2, March, 1940.

Gastroscopy is a valuable adjunct to other methods for diagnosis of gastro-intestinal conditions, and the established indications, according to the author, fall into the following five groups:

1. Patients with negative roentgen gastro-intestinal findings but in whom one still suspects the presence of gastro-intestinal disease. It has been estimated by various authors that such patients constitute from 15 to 45 per cent of a general practice. This group is important because gastroscopy is probably the only clinical method of making a diagnosis in these patients.

2. The second large group of cases in which a gastroscopic examination is indicated are those with inconsistent, inconclusive or incomplete roentgen findings. Bizarre filling and antral defects, complete or partial pyloric obstruction, deformity of the duodenal bulb without a definite diagnosis of duodenal ulcer, are all indications.

3. Patients in whom a gastric ulcer has been demonstrated radiologically. The course of the benign ulcer is better followed to complete healing, and more accurate differentiation of the malignant ulcer is accomplished by means of gastroscopic examination.

4. Patients in whom gastric carcinomas have been demonstrated radiologically. The importance of gastroscopy in this group is the confirmation of the suspected lesion, the finding of lesions not diagnosed by other methods, and in giving the surgeon more detailed information on the extent of the lesion.

5. Patients who have had any type of gastric operation for either benign or malignant lesion. This is particularly important in the patient who has a persistence or recurrence of symptoms post-operatively. Often the recurrent stomal ulcer is too small, the anatomic rearrangement too confusing or the mucosal changes too diffuse and superficial to be demonstrated by X-ray.—C. Wilmer Wirts, Jr. and B. B. Vincent Lyon.

ERNSTENE, C. A.

*Gastro-Intestinal Manifestations of Cardiovascular Disease. Medical Clinics of North America*, 24:381, No. 2, March, 1940.

Written from the viewpoint of a cardiologist, certain symptoms that would ordinarily direct attention to the gastro-intestinal tract are shown to be due to lesions of the cardio-vascular system. DYSPHAGIA may be due to aneurism of the arch or descending portion of the aorta, to enlarged left auricle, and to large pericardial effusion. ANOREXIA is a common symptom of slight or moderate congestive heart failure. With advanced failure, NAUSEA, VOMITING and FLATULENCE make their appearance—out of all proportion to such heart symptoms as dyspnoea and cough. The mechanism of production is said to be that of passive congestion of both the gastric and intestinal mucosa as well as of the liver. One should examine for enlarged heart with irregular rhythm, passive congestion of the lungs, engorged jugulars even when patient is propped up, enlarged liver with tenderness, and edema of

legs and lower back. The author warns that this same trilogy of symptoms may well be present in over-digitalization. Coronary disease may show nothing subjectively other than sensations of substernal fullness, distention or gas in upper abdomen with nausea and vomiting which become worse after meals. If improvement follows the taking of small meals, resting after meals, and the administration of nitroglycerine, it may well be expected that the electrocardiogram will show coronary disease. JAUNDICE is frequently present in congestive heart failure, and is due to depressed excretory function of liver (anoxemia of the liver cells from passive congestion) together with increased production of bilirubin. If the jaundice grows suddenly more pronounced, then infarction of the lung must be suspected. Jaundice may develop within two or three days after coronary occlusion—with enlargement and tenderness of the liver. In congestive heart failure there may be ABDOMINAL PAIN—pain or discomfort in the epigastrium and right upper quadrant because of enlarged and congested liver. The pain of angina pectoris follows exertion, improves on resting, and is confined to the retrosternal region and epigastrium. In coronary thrombosis there may be pain only in the upper abdomen with muscle spasm and tenderness. These, with fever, leukocytosis, vomiting and jaundice will possibly suggest biliary colic, perforated ulcer, acute intestinal obstruction or acute pancreatitis. To make the diagnosis, inquiry should be made about a history of "Indigestion on effort" with dyspnea and the spreading of the pain to the retrosternal area, weakness of heart tone and gallop rhythm. The diagnosis is made more clearly if there is a pulsus alternans, râles at lung bases, and a precordial friction rub which occurs in ten to fifteen per cent of cases of myocardial infarction within one to three days of onset. This latter is a valuable sign, but of even greater value is the electrocardiogram. In passing, it should be remembered that not a few cases of gall bladder disease have been incorrectly diagnosed as angina.—Henry J. Bartle.

LADD, WILLIAM E. AND GROSS, ROBERT E.

*Surgical Treatment of Duplications of the Alimentary Tract—Enterogenous Cysts, Enteric Cysts or Ileum Duplex. S. G. O., 70:2A-295, Feb. 15, 1940.*

This article was based on the authors' experiences with 18 patients with cystic lesions located along various parts of the alimentary tract. The enteric and enterogenous cysts are most common though some of the lesions are tubercular and go through the mesentery parallel to or communicating with the bowel or other lesions. They are hollow structures which have a muscular coat, usually of two layers, lined with epithelium and usually strongly adherent to the alimentary tube. The contents of a duplication depend on the kind of epithelium lining the structure and the presence or absence of necrosis of the duplication wall or a communication with the adjacent intestine. However, usually it contains a clear colorless fluid of mucoid consistency; the fluid may be hemorrhagic and murky-colored if pressure necrosis and sloughing of the lining membrane is present.

Size may range from a centimeter in diameter to the size of a grapefruit before being noticed. Mesenteric cysts are lymphatic in origin, with a thinner wall and can be easily separated from adjacent viscera. A duplication has a thicker, muscular wall and can be disconnected from the intestine only with difficulty. It is believed that they arise from a pinching off of a small bud from the gut wall with development of this segregated tissue into a cystic structure adjacent to the normal intestine.

A duplication in the alimentary tract usually occurs in children and is characterized by obstruction of the alimentary tract by regional external pressure, pain produced by distention of the cystic structure and hemorrhage because of sloughing of the intestinal mucosa. There may be difficulty in swallowing, dyspnea, epigastric fullness, colic-like pain, vomiting and perhaps signs of dehydration,

The best treatment is complete excision of the cyst with removal of the attached portion of the alimentary tract. If this is not possible, a window may be cut between the cyst and adjacent intestine for drainage or the cyst may be marsupialized and the lining cauterized with sclerosing agents. In the operative procedure, two factors must be emphasized: (1) the cystic structure and intestine have a common wall at one point and cannot be taken apart with safety; (2) the blood vessels of the contiguous alimentary tube may course over the surface of the cyst and local removal of the cyst may induce ischemia and necrosis of the intestine.—Francis D. Murphy.

DENNIS, CLARENCE AND WOOD, EARL H.

*Intestinal Absorption in the Adrenalectomized Dog.* *Am. J. Physiology*, Vol. 129, pp. 182-190, April, 1940.

The authors after noting that Harrison and Darrow had demonstrated changes in renal function when adrenal cortex extract was withdrawn from adrenalectomized dogs believed that there was suggested a general change in the characteristics of the body membranes.

To determine this absorption rates of potassium sodium and chloride were studied by introducing isotonic solutions of these ions into a segment of terminal ileum and then withdrawing them after a period of time for analysis. They found that with high sodium, high bicarbonate and low potassium diets in adrenalectomized dogs in which adrenal cortex extract had been withdrawn there was a decrease in the absorption of these ions from the chronic loops of ileum. This was reversed upon the administration of adrenal cortical hormone. The decline in the rate of absorption of the sodium ion was greater than the potassium, in some cases sodium was excreted into the gut. The authors conclude that in spite of objectively good health the behavior of the intestine in adrenalectomized dogs was not normal unless adrenal cortex extract was given.—J. Kenneth Karr.

DENNIS, CLARENCE.

*Injury to the Ileal Mucosa by Contact with Distilled Water.* *Am. J. Physiology*, Vol. 129, pp. 171-176, April, 1940.

The author of this article after observing some experiments by Vischer, Ingraham and Burns noticed that when distilled water was left in the bowel the concentration of the chloride rose to a level higher than that of an ultrafiltrate of plasma. He believed that this phenomenon was due to mucosal injury by the distilled water used. He determined to prove or disprove this belief by placing 50 cc. of distilled water in a 60 cm. low ileal loop of bowel in a waking dog and watching the chloride concentration. Several days later the same procedure was carried out, using an isotonic sucrose solution in place of the distilled water.

The author concluded that the distilled water injured the mucosa by interfering with the impermeability of the gut to sulfate and the ability of the epithelium to do osmotic work. He believes that isotonic salt solutions would be more valuable in irrigating the small bowel rather than the distilled water frequently used.—J. Kenneth Karr.

DENNIS, CLARENCE AND VISSCHER, MAURICE B.

*The Influence of Various Factors Upon Intestinal Absorption Involving Osmotic Work in the Unanesthetized Dog.* *Am. J. Physiology*, Vol. 129, pp. 176-181, April, 1940.

The authors set about to determine whether the lower ileum of the unanesthetized dog does osmotic work in absorbing NaCl against a concentration gradient from solutions containing mixtures of NaCl and Na<sub>2</sub>SO<sub>4</sub>, as it does in anesthetized dogs. This was done on 10 dogs on which Thirty-Vella loops were prepared. They concluded that in unanesthetized dogs active absorption from the lower ileum does occur; that absorption from Thirty-Vella

loops from the upper, middle and lower ileum is progressively more rapid in the order named; that excitement causes a diminished rate of absorption which is abolished by anesthesia in excitable dogs and not in placid ones; that excitement causes mucosal blanching; that the rate of active absorption is faster in chronic loop experiments than acute ones; and that food ingestion does not alter the absorption rates.—J. Kenneth Karr.

HERRIN, RAYMOND C.

*The Secretion of Ammonia by the Small Intestine of the Dog.* *Am. J. Physiology*, Vol. 129, pp. 146-154, April, 1940.

This is a study of the various factors influencing the concentration of ammonia in the juice secreted by a Thirty-Vella loop of jejunum in the dog. The author found that when the diet was changed from one containing 23 per cent protein to carbohydrate the ammonia content decreased from 27 to 74 per cent in six dogs. In 4 dogs there was a 3.8 to 6 fold increase in the ammonia content. Marked changes in the ammonia content of the juice paralleled changes in urinary nitrogen excretion rather than nitrogen intake. When glycine or glutamic acid was given intravenously there was a 42 to 164 per cent increase in the ammonia content of the juice. When urea was given there was an increase of from 22 to 130 per cent in the juice. Sodium chloride partially checked the effect of an elevated blood urea upon the juice when given intravenously. Insulin also caused a great increase and adrenalin caused variable results.

The author concluded that ammonia is secreted by the gland of the jejunum; that its concentration is dependent upon the protein metabolism of the gland cells; and that the ammonia has no physiological action merely appearing in the juice because of its diffusibility.—J. Kenneth Karr.

HUNT, VERNE C.

*Current Methods in the Management of Peptic Ulcer.* *S. G. O.*, 70:2A-319, Feb. 15, 1940.

It has been found that whether the peptic ulcer is treated medically or surgically, a permanent cure depends on the thoroughness by which gastric acidity and gastric secretion is controlled by dilution and neutralization or through quantitative reduction.

In cases of uncomplicated duodenal and gastric ulcer of short duration, medical treatment is usually effective. Surgical procedure is usually best in patients with chronic lesions, multiple hemorrhages, persistent pyloric obstruction, perforation, gastric retention or in cases where medical management has not been effective.

When acute perforation of a peptic ulcer is present, surgical procedure to close the perforation is a life-saving measure though it is not a permanent cure. Protective perforation of a duodenal or gastric ulcer is usually characterized by clinical manifestations of a subacute inflammatory process though in some cases the perforation occurs by penetrating a structure to which the ulcer base has been attached. In these cases medical treatment is resisted and surgical treatment is resorted to.

Gastric retention when due to edema of reactivation of ulcer is usually temporary and medical treatment will relieve it though it may recur. If it is caused by cicatricial pyloric stenosis or a disturbance of gastric motility, surgical treatment is necessary.

In cases of bleeding peptic ulcers, there is a question as to whether medical or surgical procedure is best. The ordinary bleeding peptic ulcer is usually treated by non-surgical methods and if the healing of the ulcer and disappearance of hemorrhages does not occur, then surgical treatment can be instigated. A massive exsanguinating hemorrhage constitutes an emergency and calls for transfusion to restore blood volume. Then age plays a part. If the patient is over 50 years of age, operation is not usually indicated during hemorrhage except if there is no im-

provement resulting from continued transfusion of 12 to 24 hours. If they have recovered from a massive hemorrhage through medical measures, surgery is advised to prevent recurrence. If the patient is under 50 and has had repeated massive hemorrhage, he should be operated on as soon as conditions permit.

When there is any doubt as to the true nature of the lesion, surgical treatment is indicated. Surgical procedures are of three types: (1) Gastro-enterostomy and gastro-duodenostomy with or without excision of the ulcer; (2) Plastic operations on the pylorus with or without excision of the ulcer; (3) Gastric resection to restore gastro-intestinal continuity. No operation should be used as a routine procedure, but the operation which best suits the situation with the greatest degree of safety should be chosen.—Francis D. Murphy.

JOHNSTON, CHARLES G.

*Decompression in the Treatment of Intestinal Obstruction. S. G. O., 70:2A-365, Feb. 15, 1940.*

In cases of simple acute obstruction, enterostomy is a successful method of decompression of the distended bowel and relieves the obstruction. However, it does not get at the cause of the obstruction and may only offer temporary relief.

The more modern method of decompression is by means of intubation. The tubes are usually introduced into the intestinal tract through the natural orifices and are about 10 feet long with an inflatable balloon at the lower end. The balloon is inflated and peristalsis propels the tube downward until stopped by obstruction to its passage. Usually a large tube is used for aspiration and a smaller tube for inflation of the balloon. Intestinal intubation helps determine the type, extent and level of the obstructing lesion, and if the tube is passed well down in the intestine, the patient may be fed a diet low in fiber content and absorption of food, fluid and salt occurs.

This method relieves the patient's distention without operation and makes it possible to delay surgery until the patient has a normal fluid and chemical balance and the difficulties encountered of operation amid distended loops is removed. The obstruction can be localized before operation through the use of small amounts of barium given through the tube for roentgenographic studies. In the treatment of adynamic ileus, there seems to be enough muscular power left in the intestinal wall to pass the tube down once the over-distention is relieved. If there is a definite organic lesion, operation is still necessary but it is much easier for both the surgeon and patient.

Certain disadvantages are connected with this procedure. There is the possibility of failure to recognize interference with the mesenteric blood supply though this recognition is not difficult to make. Difficulty is encountered in introducing the tube into the duodenum and intubation of the small intestine is thus hard work and requires constant care. Sometimes the tube causes irritation to the nose and throat and is uncomfortable, but the advantages of the procedure make up for the disadvantages.—Francis D. Murphy.

NORTH, PAUL H. AND WILBUR, D. L.

*Chemical Changes in the Blood of Patients with Pyloric Obstruction. Annals of Int. Med., XIII, 1285, Feb., 1940.*

The authors made a study of 151 patients having an ulcer or cancer of the stomach or an ulcer of the duodenum, resulting in a pyloric obstruction, for the purpose of finding what effects certain factors had on blood chemistry.

Their work appears to confirm the rather widely accepted view that pyloric obstruction tends to lower plasma chloride values. They suggest but offer no data establishing the importance of other factors; among these are a shift of chlorides from tissues to blood or from corpuscles to plasma, changes in renal function altering chloride

elimination, plasma concentration, as well as variations in chloride content of food and drink. Neither did their work indicate the mechanism of alteration of blood urea values in pyloric obstruction; the action of some toxic substance, the effect of hydration on body protein destruction, the role of impaired kidney function, of hypochloremia or of alkalosis are left undetermined. They concluded that the type of lesion causing the obstruction was not significant, nor was the presence or absence of hydrochloric acid a determining factor. They found that changes in plasma chlorides and blood urea did not run uniformly parallel until extreme value changes were reached. They think that if plasma chlorides are estimated there is little reason for determining the CO<sub>2</sub> combining power of blood plasma. A warning to the clinician is sounded to not be guided by chemical values of blood studies since a deficiency of chlorides in the tissues may exist in the presence of normal values in the blood. The value of intravenous injections of a physiological solution of sodium chloride and a 5 to 10 per cent solution of dextrose is emphasized.—Virgil E. Simpson, Louisville, Ky.

KAUFMAN, R. E.

*Trichiniasis: Clinical Considerations. Annals of Int. Med., XIII, 1431, Feb., 1940.*

This contribution covers material from the Lenox Hill Hospital, New York City, occurring sporadically as a series of 35 cases. The literature is only briefly reviewed but an exhaustive bibliography is given. Abstracted case records of twelve of the group are given. The condition is described as the only melazoan infestation in the human regularly accompanied by fever and characterized as a major public health problem. It is stated that it has been found in from 10 to 25 per cent of autopsies when searched for. The mortality has varied to as high as 30 per cent, with an average of 10 per cent in outbreaks. In the life history the pig is found to be the most common carrier and "hot dogs," now so popular, is a common offender. Thorough cooking of meat is the answer. The death temperature point of the parasite is 55 C. (126 F.). The Bureau of Animal Industry recognizes 58.3 C. (137 F.) as minimum temperature for cooking, but a more practical method is Cameron's that "pork should be cooked until the natural color is gone." Federal meat inspection does not now require a microscopic examination for the parasite. Salt or smoke curing or pickling usually kills the worm.

That 50 per cent of some groups reported had a respiratory tract involvement, including pneumonia, pleurisy and hemoptysis; that affections in the nervous system such as paralysis of eye and skeletal muscles, encephalitis, meningitis are not uncommon; that myocarditis, thrombosis, nodal arrhythmia and congestive failure are not uncommon cardio-vascular symptoms; that these and more obtain may surprise many clinicians.

Another surprise is that a Widal test may be positive. An intradermal test has been developed and a precipitin test is discussed. Biopsy study gives a high per cent of diagnoses, and a diagnosis is not always easy. Specific therapy has not been successful; even sulfanilamid has been tried and failed. In the laboratory ergosterol and calcium have hastened cyst formation and calcification. Symptomatic and supportive treatment remains the chief reliance.—Virgil E. Simpson, Louisville, Ky.

BROWN, RALPH C.

*Spastic Irritable Bowel. Medical Clinics of North America, 24:193, No. 1, Jan., 1940.*

Isolate your true pathology or functional disorder, examine the stool and avoid the word "Colitis."

Abdominal pain is most frequently caused by SPASTICITY which originates from three groups of irritants: (a) continued use of cathartics and enemas causing inflamed mucous membranes and irritable nerve endings.



95% of constipation cases can have normal bowel movements by very simple measures; (b) *lack of starch and sugar digestion* in the small intestine followed by fermentation in the caecum causes chronic irritation of the mucous membrane with a spastic irritable bowel with an acid stool containing starch. An infrequent type of chronic putrefactive colon caused by increased protein diet yields gram negative bacteria and alkaline feces and can be remedied by balancing the diet; (c) *hyperirritability of the vegetative nervous system*. The neuro-muscular action of the bowel is not stimulated by chemical irritants, as in the cathartic and fermentative types, but by the sensitivity of the nerve plexuses in the bowel wall, secondary to fatigue, fear, anxiety and mental stress. The undernourished type, with weak flabby muscles, narrow epigastric angle, low lying abdominal viscera, cold clammy hands and feet and low blood pressure, have small ribbon or ball stools, and give varied abdominal symptoms aggravated by any emotional disturbance. In women these are worse during the menstrual period.

**THE NERVOUS TYPE OF IRRITABLE BOWEL** is found in individuals who have normal bowel activity when in pleasant surroundings with no worries. Mental fatigue, strain or excitement causes flatulence, abdominal pressure and constipation with loss of tone and rhythm of the colon. They suspect cancer, and many an innocent appendix has been removed in their search for relief. Two weeks of rest and play would have served a better purpose. Quoting F. Ehrlich, "It is a well known fact that 30 to 40% of patients operated upon for chronic appendicitis retain their symptoms after the operation, often to an increased degree." Functional bowel disorders are responsible for a great many abdominal pains and should be given a great deal of consideration in abdominal diagnosis.

**TREATMENT** is given to remove the cause. *Cathartic type*: Rest this bowel, stop enemas and cathartics, give a bland diet, massive doses of belladonna and use continuous hot moist packs covering the entire abdomen. In less severe cases: eliminate physics, give a diet with a large quantity of residue and sweet oil retention enemas on retiring when necessary. Avoid cold drinks! Instruct the patient in the anatomy and physiology of the colon and explain the difference between constipation and small daily stools. Protect the colon against chemical and thermal irritants.

**THE FERMENTATION TYPE** will improve with the removal of carbohydrate from the diet with a gradual return after a rest period.

**PATIENTS CONSTITUTIONALLY BELOW PAR** with a long history of medical and surgical treatment become undernourished, introspective and skeptical of ever obtaining relief. Hospitalization, medical diplomacy and skill are essential in these cases. They must be treated individually. Soothe and encourage them; restrict the diet and increase it slowly as conditions permit; apply hot packs to the abdomen; and prescribe tincture of opium and large doses of belladonna.—C. H. Arnold and B. B. Vincent Lyon.

COLLINS, E. N.

*Duodenal Drainage: Indications and Technic. Medical Clinics of North America, 24:473, No. 2, March, 1940.*

The author, in recent years, has employed duodenal drainage in an increasing number of cases and states that it has given information which could be obtained in no other way. He believes that if we are to make an early diagnosis, more widespread use of duodenal drainage is important, particularly in borderline cases.

In discussing the technique of duodenal drainage the author emphasizes the need of great care and exactness in the technique used; he emphasizes the experience of the examiner and the value of experience in the interpretation of what the examiner sees. He states that positive findings can be accepted with greater certainty than negative findings, and points out that when there is an absence of con-

centrated bile with the gall bladder present and when drainage diagnosis is indeterminate or not consistent with clinical expectancy, that repeated recheck examinations should no more be neglected than is the case with other examinations.

After appraising the value of cholecystography the author believes that insufficient emphasis has been placed on its limitations, and points out that normal cholecystographic findings do not exclude the presence of a significant cholecystitis. In such cases in which clinical suspicion of biliary disease is entertained he advocates that the cholecystographic negation of disease should not be accepted until two or more duodenal drainages have yielded normal findings. He also points out that non-visualization does not necessarily indicate a pathologic gall bladder.

Dr. Collins relates his favorable experiences with duodenal drainage both in diagnosis and treatment and appends a sufficient bibliography in support of his opinion.

As to diagnosis he finds duodenal drainage has been helpful in six groups and his article discusses this quite fully. (1) Suspected biliary disease after cholecystectomy—"the post cholecystectomy syndrome." (2) With gall bladder intact, suspected biliary disease complicated by jaundice. (3) With gall bladder intact, suspected biliary disease but without jaundice. (4) Suspected pancreatic disease. (5) Certain diseases of the liver, such as biliary cirrhosis. (6) Postoperative appraisal of state of biliary tract.

He points out the significant and the suggestive abnormal findings on duodenal drainage both in the gross examination of the bile and its microscopy and bacteriology in correlation with the roentgen findings.

Regarding treatment the author has had favorable results with duodenal drainage in pancreatitis; "catarrhal jaundice"; biliary dyssynergia; non-calculous biliary tract disease; and intractable urticaria especially if combined with vaccines. In discussing the treatment of gall bladder disease, he re-emphasizes the difference in giving hypertonic magnesium sulfate by mouth and by duodenal tube and its disadvantages if orally administered.

Dr. Collins summarizes his article with the following conclusions:

1. The increasing use of duodenal drainage in recent years, in correlation with cholecystography as well as with the clinical and other findings, has proved to be an important diagnostic procedure under the circumstances mentioned.

2. The most important indications for duodenal drainage are the instances where the gall bladder has been removed, where jaundice of a sufficient degree to contraindicate the use of cholecystography exists, and when both clinical and cholecystographic findings are inconclusive.

3. In patients having operations subsequent to duodenal drainage, the operative findings confirmed the findings by duodenal drainage in 84 per cent of all cases to date.

4. Since routine autopsies in various countries have shown that half of the persons above the age of thirty years had pathologic changes in the gall bladder and approximately 20 per cent had gall stones, the more common use of duodenal drainage should result in earlier diagnoses and earlier operations, if medical management is not appropriate, before pathologic processes have extended so widely that surgery cannot be expected to relieve the patient's symptoms.—B. B. Vincent Lyon.

REYNOLDS, L., MACY, I. G., HUNSCHER, H. AND OLSON, M. B.

*The Gastro-Intestinal Response of Average Healthy Children to Test Meals of Barium in Milk, Cream, Meat and Carbohydrate Media. Am. J. Roent. and Rad. Ther., 43:517-532, April, 1940.*

The authors made complete and thorough roentgenologic studies of the gastro-intestinal tract in average healthy

children to determine the gastric motility, its variations, effect of carmine and variations in response to different types of milks. Five different types of meals were utilized in the same subjects. Barium meals were given with varying fat, carbohydrate and protein content. They observed that the emptying time of the stomach with the water meal averaged 1.9 hours; with milk and glucose averaged 3.1 and 3.3 hours; with meat and cream averaged 5 and 4.8 hours respectively. Their findings indicate that the type of meal has a specific motor effect upon the egression of the meal through the pylorus. The results of their studies are in agreement with those involving the osmotic pressure change produced by sugar solutions on pyloric action and suggest that osmotic pressure above or below isotonicity definitely influences pyloric action and gastric evacuation, i.e. the greater the hypertonicity of the test meal the slower the gastric emptying. They also show that a hypertonic solution does cause an increase in the volume of the gastric contents.

The authors observed that the milk-barium meal produce only an initial delay in the passage of meal through the pylorus. The cream-barium meal showed that the intensity of the control of the pyloric action is proportionate to the fat content. They point out that with the protein meal (baked meat-loaf) there is an accompanying high gastric acidity for the initial digestion, and that the variation in acidity is compensated in the duodenum as to render the content neutral or only slightly acid.—Maurice Feldman, Baltimore, Md.

MEYER, JACOB.

*The Management of Diseases of the Gastro-Intestinal Tract in the Aged. Medical Clinics of North America, Jan., 1940.*

This very thorough article covers the subject from many viewpoints, including the frequency of gastro-intestinal symptoms; the infrequency of gastro-intestinal organic disease, and the pathology in other organs giving referred gastro-intestinal symptoms. The author goes on to show how carbohydrate digestion in the small intestine by pancreatic amylase compensates for the decrease of salivary ptyaline due to cellular atrophy.

Increased achlorhydria with less pepsin and trypsin due to senile atrophy are balanced by a normal concentration of lipase and low concentration of proteolytic enzymes for protein digestion.

The best results are obtained by allowing elderly people to choose their own diet, even though they incline toward a heavy carbohydrate balance due to increasingly difficult mastication.

Loss of appetite increases with the atrophic changes in sight, smell, taste, and salivary and gastric secretions, and, as the teeth become less useful for proper mastication.

The appearance of the tongue, along with the fear of cancer of that organ, have a psychic effect on the aged which should not be considered too lightly.

Quoting Ivy, "above the age of 60, thirty-five per cent do not secrete acid when they eat a meal, and twenty-eight per cent do not respond to histamine," you should suspect cancer when digestive discomfort is related to food. But actually cancer is seldom found above the age of 70.

Peptic ulcer is very rare unless it is secondary to other pathology, and hemorrhage and perforation are severe complications because of arteriosclerosis. With gastric symptoms, always investigate the heart.

Appendicitis is possible but with atypical symptoms. Gall bladder diseases usually give an elevated icterus index, but chills, fever and headache may be absent.

Constipation and fecal impaction are commonly found with the muscle atrophy. Diverticulosis with pus in the feces makes one think of cancer, but it often subsides as the inflamed diverticula become normal.—Clifford H. Arnold and B. B. Vincent Lyon.

CONN, JEROME W.

*Interpretation of the Glucose Tolerance Test. Am. J. of Med. Sciences.*

Carbohydrate restriction or starvation lessens the ability to utilize carbohydrate. This should be applied in clinical medicine. In the differential diagnosis between non-diabetic and diabetic glycosurias, the glucose tolerance test should take into account the influence of the previous dietary regime. After a period of starvation, hyperglycemia, glycosuria and delayed removal of glucose from the blood stream, have been observed. A few days of high carbohydrate feeding will eliminate this factor. Those who are poorly nourished are more susceptible to short periods of carbohydrate restriction. These cases are cited to indicate how an erroneous diagnosis of diabetes mellitus may be made. Undernourished individuals may require more than five days of high carbohydrate feeding to effect complete return of normal carbohydrate tolerance. The writer describes cases in which renal glycosuria was thought to be true diabetes and he contends that glucose tolerance tests must be preceded for several days by the ingestion of an adequate Standard Preparatory Diet of 80 gm. of protein, 300 gm. carbohydrate, 2800 calories and a sample diet is given.—Allen Jones, Buffalo, N. Y.

RITVO, M. AND McDONALD, E. J.

*The Value of Nitrites in Cardiospasm. (Achalasia of the Esophagus). Am. J. Roent. and Rad. Ther., 43: 500-508, April, 1940.*

The authors point out the present conception of the etiology of cardiospasm. The condition is due to a defective or absent relaxation of normal tonicity rather than a spasm, which results in a failure of the normal mechanism, producing the so-called idiopathic dilatation of the esophagus. They direct attention to the analogy of Hirschsprung's disease to this condition, which is also due to an imbalance of the parasympathetic and sympathetic influences.

Ritvo and McDonald utilized the nitrites to abolish the obstruction in cardiospasm. Since, as pointed out by McGowan and Butsch, amyl nitrite has the effect of relaxing the ampulla of Vater, Ritvo and McDonald used this drug for the relief of achalasia with gratifying results. After the inhalation of the vapor there occurred almost immediate disappearance of the stenosis of the lower esophagus. Nitroglycerine was also used and found to produce satisfactory results. The average dose is 1-100 gr. tablet placed on floor of mouth. The effect of amyl nitrite was quicker than nitroglycerine, probably due to the method of administration, but nitroglycerine was more variable and less effective than amyl nitrite.

The authors emphasize that the nitrites have proved of no permanent curative value, but the drugs have a definite though limited application. Tablets of sodium nitrite and erythrol tetranitrate were tried with slight and variable effect.

In the treatment of cardiospasm the passage of bougies may be facilitated by the use of nitrites. To the roentgenologists the nitrites are of definite value, in serving to increase the ease and accuracy of roentgen studies. The authors mention the fact that the nitrite action is of short duration.—Maurice Feldman, Baltimore, Md.

BARNETT, T. NEILL.

*Polyps of the Colon and Rectum. Southern Med. J., 33:242-245, March, 1940.*

The polyp is a new growth, adenomatous in character, arising from the normal intestinal mucosa and consisting of epithelium and connective tissue elements of the organ from which it arises. The etiology is obscure. Those arising from the intestinal tract are comparatively rare. The acquired adult type may be single or multiple. The rare congenital type consists of a diffuse polyposis. Intestinal polyps under two centimeters in size and having long peduncles are usually benign. Those from four to six centi-



meters in size with or without long pedicles are usually benign in the beginning but are prone to malignant change. Those without a pedicle are potentially cancerous quite early in their development. The symptoms of polypoid disease vary from none in the early stages to profound diarrhea, passage of blood or intestinal obstruction in the late stage. X-ray demonstration is essential for those in the right half of the colon. The only effective X-ray examination is by the use of the double contrast barium enema and subsequent air injection. Fortunately, that area of the colon where the X-ray is of practically no value, the anus to the rectosigmoid, sigmoidoscopic examination is of the most value. When using the sigmoidoscope it is important to visualize the superior as well as the inferior surface of Houstons' valves. Since biopsy gives uncertain findings depending upon what part of the growth is secured for examination, and since its trauma may incite the growth to greater activity or metastasis such procedure is not recommended. On the other hand since every polyp starts as a benign growth and since malignant change is frequent the removal of every polyp should be an unchanging rule. If accessible through a sigmoidoscope they should be removed by fulguration which seals the lymphatics and leaves a soft flexible scar. If not accessible through a sigmoidoscope they should be removed by as radical a procedure as is necessary. Four interesting illustrative cases are reported.—J. Duffy Hancock.

HUNT, C. J.

*Extensive Radical Resection for Malignant Disease of the Stomach. Southern Med. J., 33:234-237, March, 1940.*

The reasonably satisfactory results obtainable by the radical operation of extensive subtotal resection of the stomach for malignant disease make this procedure as important as the simpler one of partial gastrectomy for lesions in the accessible prepyloric area. There are three principal indications for the operation: (1) large ulcerative lesions in the mid-portion of the stomach with extensive associated induration which can be shown to be inflammatory in that it yields to separation, (2) primary prepyloric lesions with extensive glandular involvement along the greater and lesser curvatures, and (3) benign ulcerative lesions or primary ulcerative malignant disease lying high on the lesser curvature or on the posterior wall of the stomach.

Since there are no early pathognomonic signs and symptoms of cancer of the stomach radiologic examination, repeated after a short interval if necessary, is of extreme importance and should be a routine measure not only for those approaching the mid-period of life with gastric disorder for the first time but also for those giving a long history of gastric upsets which no longer yield to medical management. Important as X-ray findings are in regard to diagnosis they are not an accurate index of operability and all patients, regardless of age, who can be brought into suitable physical condition should be explored. The only contraindications to operation are extremely high lesions, large lesions with definite fixation, large nodular liver with or without ascites or jaundice, infiltration of the umbilicus or rectal shelf, firm fixed glands above the left clavicle and grave coexisting organic disease.

The presence of lactic acid and Boas-Opplar bacilli on gastric analysis indicate the preoperative need of hydrochloric acid. Anemia, dehydration and reduced glycogen reserve should be corrected by transfusions, forced fluids and glucose administration and gastric dilatation by frequent lavage. Spinal anesthesia is preferred but cyclopropane or ether are satisfactory. The best surgical approach is the left rectus or left paramedian incision. A Polya type of anastomosis will usually be necessary. The procedure can be done in two stages. Continuous siphonage through a nasal tube with occasional small amounts of water by mouth are routine post-operatively.

Aspiration pneumonia is the most fatal post-operative complication. Satisfactory bronchial aspiration by bronchoscopy is indicated. Peritonitis can be avoided by adequate pre-operative preparation of the infected stomach, satisfactory suturing especially of the duodenal stump and avoidance of contamination at operation.—J. Duffy Hancock.

WOLLBACH, GUNTER.

*Sur les Actions Inflammatoires des Substances Sécrétoires dans le Tube Digestif. (The Inflammatory Action of Secretory Substances in the Digestive Tract). J. de Physiologie et de Pathologie Générale, 37:978, No. 3, 1939-1940.*

The inflammatory reaction of secretory substances were studied on white mice. Animals weighing about 15 g. were used. Daily administration of 1/3 the human dose was carried out for four days. The mice had been fed on white bread and water for one week preceding the experiment. The signs of inflammation varied from a slight lymphocytic accumulation to a marked exudation of lymphocytes, granulocytes and cellular debris. No inflammatory changes in the intestinal mucosa could be observed following the use of simple inhibitory substances. The effects of the secretory substances varied. Some produced a real inflammation, but with others, the opposite was encountered. It is noteworthy that the secretory substances of the sympathetic group did not provoke any inflammatory reaction at all.

The three basic food-stuffs were next studied, and were found to produce a cellular reaction of an inflammatory nature. The true stomachies did not produce any evidence of inflammation in the gastric mucosa, even when resulting in a copious gastric secretion. Changes were noted, however, in the duodenum and colon. The author concludes that certain secretory substances do produce changes in the intestinal mucosa of an inflammatory character. Many of these are accompanied by a hypersecretion. The reaction is not uniform in all segments of the digestive tract, nor is there any quantitative relationship between the dose of stimulant used, and the severity of the reaction produced.—Philip Levitsky.

DE FINE LICHT, ERIC.

*Roentgen Diagnosis of Ileus. Acta Radiol., XXI, 1:32, Feb., 1940.*

The roentgenological diagnosis of ileus, when based on the findings of a fluid level, is on the whole of considerable diagnostic value. However, the mere accumulation of gas in the small intestine does not justify a diagnosis of ileus. For the prognosis and as indication for operation it is of no particular value, but it becomes valuable if the examination is repeated, because this makes it possible to observe any changes in the degree of severity of the roentgenologic picture. Whether an ileus is paralytic or mechanical cannot be determined with certainty by roentgen examination. In cases of colonic ileus, the barium enema will, however, not infrequently settle the question.

Roentgen pictures similar to those in ileus are often found after an operation and in cases of abdominal trauma the roentgenological examination may reveal very considerable changes resembling ileus. The absence of a fluid level is rare in ileus, and if both fluid level and abnormal gas accumulation are absent, the possibility of existing ileus is slight.—Franz J. Lust.

KLEIN, I. AND HOCHBAUM, W.

*Stenosing Esophagitis Associated with Duodenal Ulcer. Am. J. Roent. and Rad. Therapy, Vol. XLII, 5:724-725, Nov., 1939.*

Klein and Hochbaum report a rare case of a coincidence of tumor forming esophagitis and duodenal ulcer. Shortly after gastro-enterostomy a direct examination of the esophagus showed an extensive tumor mass in the lower

part of the esophagus. The microscopic examination revealed diffused necrosis, numerous hemorrhages, widespread granulation tissue. Many blood vessels were noted.

One year later a diaphragm across the lumen with incomplete stenosis was found. The stricture was dilated with bougie with the result that the patient improved and gained twenty-eight pounds in weight.—Franz J. Lust.

STETTEN, DEWITT.

*Duodenojejunoscopy for Congenital, Intrinsic, Total Atresia at the Duodenojejunal Junction. Ann. Surg., 111:4-583, April, 1940.*

Stetten reports the case of a successful performed operation on a 3 days old child with total obstruction at the duodenojejunal junction. The clinical symptoms in this case were similar to all those with high obstruction from birth if the lesion is below the papilla. The child could not retain any feedings and vomited bile stained material. Only a few meconium stools had passed. It became increasingly jaundiced and lost weight.

The roentgenological examination showed a considerably dilated stomach with active peristalsis, a wide open pylorus and tremendously distended duodenum with complete obstruction.

At operation, the roentgenological findings were confirmed and a lateral duodenojejunoscopy was performed which was very difficult because of the extreme disproportion between the size of the duodenum and the jejunum. Besides an arrested rotation of the colon with a primitive cecum was found.

The child recovered and is now 3 years old. Roentgenological examination still reveals a dilated stomach, a persistent distension of the duodenal loop with satisfactory emptying of the stomach and functioning of the anastomosis.

The importance of early diagnosis and the possibility of operative help on these cases is stressed.—Franz J. Lust.

HINKEL, CHARLES L.

*Spontaneous Pneumoperitoneum Without Demonstrable Visceral Perforation. Am. J. Roent. and Rad. Therapy, Vol. XLIII, No. 3, March, 1940.*

Spontaneous pneumoperitoneum usually results from perforation of a viscus. Two cases have previously been reported in which no cause for the free gas within the abdomen could be found.

A case of spontaneous pneumoperitoneum, which lasted twenty-one days, in a woman, aged seventy, is reported. No evidence of peritonitis or of disease of a viscus was found. Lipiodol instilled into the bronchi disclosed what appeared to be a bulla in contact with the thin, eventrated left diaphragm. As no other explanation for the pneumoperitoneum could be found, the possibility that air may have entered the abdomen by passing from this bulla through the thin diaphragm is suggested.—Franz J. Lust.

TAUB, SAMUEL J.

*Treatment of Allergic Diseases of the Aged. Clinics of North America, Jan., 1940.*

Bronchial asthma, perennial rhinitis and chronic urticaria occur more particularly in the years past middle life.

1. Family history of other allergic disturbances.
2. History of previous eczema, urticaria, asthma or food sensitivity.

3. Positive onset, as seasonal hay fever, due to pollens.

Bronchial asthma with a past history of allergy, seasonal coryza, even though slight rhinitis or urticaria, often will later develop a bronchial asthma caused by inhalant groups. Elimination of the causative factor, found by skin scratch and intradermal tests, with a potent extract injection.

With no history of allergy, these patients negative to allergic tests, seem to have more secretion and less spasm than the allergic patients and present a very grave prog-

nosis. Clear the mucus and shrink the swollen mucous membrane to relieve the symptoms. In perennial rhinitis take a very thorough history as this may be allergic of menopausal in origin. In treatment use complete rest and try to avoid or correct any causative agents.

1. Urticaria due to focus of infection.
2. Urticaria due to certain drugs.
3. Urticaria due to specific foods.
4. Urticaria due to sensitivity to articles of clothing, as wool, silk or dyes in wearing apparel.
5. Urticaria due to physical agents: heat, cold or the rays of the sun.
6. Urticaria due to skin parasites: trichophyton or scabies.
7. Urticaria due to endocrine dysfunction of the ovary or thyroid.

Urticaria is often caused by absorption of undigested proteins. If possible, find the allergic substance and eliminate that from the patient's diet, or if due to endocrine dysfunction, supply the deficiency.

Where hypochlorhydria exists the wheal is rapid in formation, whereas, in hyperchlorhydria the wheal is much slower in formation. For this reason hydrochloric acid is often a great help in relief in urticaria cases.—Clifford H. Arnold and B. B. Vincent Lyon, Philadelphia, Pa.

KEETON, ROBERT W.

*The Treatment of Senile Diabetes. Medical Clinics of North America, Jan., 1940.*

Diabetes is most often found in males at age of 51, females at 55.

In this very thorough discussion of cases, Dr. Keeton demonstrates the ability to oxidize glucose and the quantity which can be adequately handled; the hypoglycemic reaction in arteriosclerosis; gangrene and its possibilities, and the lack of calcium metabolism which is found in elderly patients, but more so in the diabetic.

Staphylococcal infections in the senile diabetics offer a very grave prognosis.—Clifford H. Arnold and B. B. Vincent Lyon, Philadelphia, Pa.

FONTS, PAUL J., HELMER, OSCAR M. AND LEPKOVSKY, SAMUEL.

*Nutritional Microcytic Hypochromic Anemia in Dogs Cured with Crystalline Factor 1. Am. J. Med. Sc., p. 163, Feb., 1940.*

"Puppies maintained on a purified casein diet apparently deficient only in Factor 1 (rat antidermatitis factor, Vitamin B<sub>6</sub>) developed severe microcytic hypochromic anemia. They also failed to grow properly and 3 of 4 animals exhibited generalized convulsions. Addition to the diet of a concentrate prepared from rice bran and containing Factor 1 cured the anemia, but in one animal, in spite of this the convulsions continued." Chick, Macrae, Martin and Martin reported similar findings in young pigs. They fed liver eluate which contained Factor 1 which brought about resumption of growth, cure of anemia and disappearance of convulsions. The authors wished to ascertain whether the substance in rice bran extract and liver eluate were identical and after careful work they found "that the material (Factor 1) which cures rat dermatitis is identical with that which cures microcytic hypochromic anemia in dogs."—Allen Jones.

MCKITTRICK, LELAND S. AND SARRIS, PETER S.

*Acute Mechanical Obstruction of Small Bowel: Its Diagnosis and Treatment. N. Eng. J. of Med., 222: 611-622, 1940.*

Having been brought up in the school which tended to favor early surgical treatment in obstruction of the small bowel, the authors feel that a review of that method was necessary at this time when the conservative treatment

with the Miller-Abbot tube was gaining marked prominence.

In reviewing 136 cases treated during the past fifteen years they include only those cases of definite acute mechanical obstruction. In the history of these cases eighty per cent were shown to have had a previous operation. The commonest symptoms were pain, vomiting, cessation of bowel movement or passage of gas. Almost three-quarters of the cases showed evidences of obstructive peristalsis elicited with a stethoscope. The most helpful of all the laboratory findings was the so-called "scout" X-ray film of the abdomen.

The authors feel that they are unable to differentiate the early stages of strangulation from simple intestinal obstruction.

The end result of the treatment of these cases was analyzed and showed that most of the deaths occurred in patients over seventy years of age following operation. The mortality was also influenced by the absence of a previous operation. (In these cases operation was usually delayed. In cases with previous operation surgical intervention was performed sooner, because obstruction was thought of earlier).

The patient who was operated on within twenty-four hours of the onset of obstruction had nine chances out of ten of requiring a simple lysis of a point of adhesion. After forty-eight hours have elapsed immediate operation should not be undertaken. A factor which adds to the difficulty of treatment was the presence of distention of the small bowel which interfered with the surgeons technique.

In the treatment of these cases the authors conclude that after the institution of relief for dehydration and chemical imbalance due to vomiting, a double lumen tube should be passed and if the case is not more than forty-eight hours old operation is indicated. If, however, the case is over forty-eight hours old and there is absence of signs of strangulation or if the patient is over sixty years of age and in fairly good condition, delay or non-operative treatment is indicated.—Henry H. Lerner, Boston, Mass.

FLEET, GEO. A.

*Displaced Gastric Mucosa as a Cause of Massive Rectal Hemorrhage. Can. Med. Assoc. J., 42:216, March, 1940.*

The author reports a case of massive rectal hemorrhage in a boy age 6½ years, in whom at operation was found:

(1) A Meckel's diverticulum located 18 inches from the ileocecal valve, measuring 1½ inches by 1 inch in diameter; the mucosa of which showed ectopic gastric tissue on microscopic examination.

(2) A perforation on the anterior mesenteric border of the small bowel, three feet proximal to the ileocecal valve. The perforation occurred along the distal margin of an area of ectopic gastric mucosa, likewise confirmed by microscopic examination. The ectopic gastric mucosa completely encircled the bowel immediately proximal to the perforation. A successful primary resection of both lesions resulted in an uneventful recovery. In the microscopic sections taken from the small bowel specimen, typical gastric fundal mucosa was found in which the glands showed both chief and parietal cells. The author discusses the various theories to account for epithelial heterotopias of the alimentary tract.—Thomas A. Johnson.

TURELL, ROBERT AND MARINO, A. W. MARTIN.

*The Value of the Sedimentation Time in Suppurations of the Anorectal Tissues. Am. J. Clin. Path., 10:300-305, April, 1940.*

The authors utilizing the well known phenomenon that the rate of sedimentation of the erythrocytes is accelerated in patients who harbor suppurative disease performed this test in cases presenting anorectal disease.

They point out that ordinarily perianal and perirectal abscesses are usually readily diagnosed, but in obscure

suppurations in the anorectal tissues their recognition may at times be difficult or delayed. They invariably found an accelerated sedimentation rate in cases of suppurative lesions in the anorectal tissues and normal rates in non-suppurative lesions.

As an important differential means, acute fissures and thrombosis of hemorrhoidal vessels may be excluded by this test. They emphasize that the sedimentation test is most valuable in establishing the absence of a suppurative anorectal condition.

The authors cite a few cases demonstrating the sensitivity of the test as correlated with the clinical picture. They recommend the employment of the test prior to the injection of oil soluble anesthetics in the ambulatory treatment of anal fissures, in order to detect hidden suppurations. The test is also useful in the management of psychoneurotic patients who have exaggerated anorectal complaints in the presence of minimal disease.—Maurice Feldman, Baltimore, Md.

LOCKHART-MUMMERY, J. P.

*War Wounds of the Large Intestine. Brit. Med. Jour., 1:451-454, No. 4132, March 16, 1940.*

Lockhart-Mummery points out that casualties with colon wounds offer greater difficulty because they are gravely shocked; have had considerable loss of blood; the wounds are not only grossly septic but contained large masses of dead tissue.

The author cites Drummond's experience in the former war, who reported 16 cases of gunshot wounds of the rectum and colon, 14 of which had died. It was Drummond's opinion that the only hope lay in immediate operation and free drainage, accompanied by the establishment of a temporary colostomy.

Lockhart-Mummery emphasizes that fecal fistulae combined with gross sepsis and comminuted fractures of the pelvis or spine were common. He cites a number of unusual cases of colonic wounds, and stresses the importance of immediate temporary colostomy when considered necessary, and points to the fact that there is a high mortality from wounds of the colon.

In a discussion of this presentation Charles Gordon-Watson stated that wounds of the colon are not often met without wounds of the small gut and other viscera. The colon wounds were often large and ragged and extremely difficult to close. They are frequently complicated with wounds of the spinal column and cord. He gives four reasons why better results would be obtained in this war than in that of the last. (1) great advance in anesthesia, (2) blood transfusion service, (3) reduction of infection by the early use of sulphanilamide, (4) acceleration of operation by the use of suction for clearing field of blood.—Maurice Feldman, Baltimore, Md.

BOCKUS, H. L., TUMEN, H. AND KORNBLUM, K.

*Diffuse Primary Tuberculous Enterocolitis: A Report of Two Cases. Ann. Int. Med., XIII, 1461, Feb., 1940.*

The authors review the literature, stressing its inadequacy, and report two cases in some detail, including very good X-ray studies. Both patients were young males and while 15 and 14 when studied, the onset was estimated to have been at 10 and 13. No contacts were determined; the bacilli were of human strain in each; points of partial obstruction were found in one, none in the other; the clinical picture of one was toxic, obstructive, the other a nutritional deficiency; X-ray study showed lesions in both. The necessity for repeated examinations of stools is stressed, believing that even in extensive involvement germs may be absent for rather long periods. Steatorrhea is stated to be an early and common finding in several types of enteritis when severe enough to disturb motility or materially lessen absorption. It is thought that the areas of constriction found in the small bowel always precede dilatation, and spasticity was not inconspicuous evidence.

The need for a careful differential diagnostic study in all so-called regional ileitis is mentioned, though it is not thought that any large per cent of such cases are primarily tuberculous. Another feature of interest is the finding of healed lesions at necropsy of the fatal case. The extent of involvement of the intestinal tract is, perhaps, the most interesting feature of these two cases. Together they present lesions beginning with the distal duodenum and ending in an involvement of the entire colon as a primary intestinal tuberculosis.—Virgil E. Simpson, Louisville, Ky.

POLYA, EUGENE.

*Re-establishment of Gastro-Intestinal Passage After Gastric Resection. S. G. O., 70:2A-270, Feb. 15, 1940.*

There are 37 different ways in which anastomosis may be carried out following gastric resection. The operation of choice will vary as to the anatomy found and the extent of pathologic process. Surgeons must keep in mind the perfection and durability of the operation as well as safety of the cure.

The nomenclature of these operations needs classification; first, should be the form of anastomosis as end to side, side to side, etc.; second, the part of the intestine used for connection as gastro-duodenostomy, and third, any special procedures as antecolic or retro-colic; inferior or superior.

Procedures of the various operations are discussed in detail and would have to be studied with great thoroughness by the reader to fully understand them. In general, he believes a gastro-duodenostomy is to be preferred to gastrojejunostomy. The reason for this is that it more closely resembles the normal stomach contour and decreases the chance of intestinal obstruction. To perform this operation the stomach stump is prepared as a tube so that there will be a circular anastomosis which is reinforced with serosa. If for some reason the end to end gastro-duodenostomy cannot be done, the second choice would be retro-colic partial inferior end to side gastro-jejunostomy. In cases where the stomach stump is so small that the retro-colic operation cannot be done, the ante-colic anastomosis is done. In the ante-colic procedure, the failures are more common but are much easier to remedy.—Francis D. Murphy.

HARTSOCK, C. L.

*Headache of Gastro-Intestinal Origin. Medical Clinics of North America, 24:341, No. 2, March, 1940.*

Hartsock points out that gastro-intestinal upsets and dysfunctions that precede, accompany, or follow headache are more likely to be an associated rather than a causative factor.

He observes that in the so called Bilious headaches, the headache usually precedes the nausea and vomiting; and draws the conclusion that the headache, nausea and vomiting have the same etiologic factor.

The statement is made that most gastro-intestinal symptoms are secondary to the factors causing the headache itself. Care is taken, however, not to discard "toxic states" as exciting factors.

The author cites three possible conclusions after careful analysis of the cause and effect: (1) the headache is primarily in the central nervous system with the gastro-intestinal symptoms secondary; (2) the exciting factor may not be located in either system, and the symptoms found in both may be reflexly produced; (3) the headache may really be the result of some organic or function gastro-intestinal disturbance. Hartsock gives most credence to his first conclusion, and least to the third.

All other possibilities must be considered first when searching for the cause of headache, and the gastro-intestinal tract considered as a last resort when all else is negative. Priority in cases of headache is given to the oculist, neurologist, allergist and syphilologist even when associated with gastro-intestinal disturbances.

The author is to be commended for the logical interpretation of his observations.—E. Sigmund LeWinn and B. B. Vincent Lyon.

THOMAS, J. W. AND JOHNSTON, C. R. K.

*Headaches of Allergic Origin. Medical Clinics of North America, 24:285, No. 2, March, 1940.*

The authors stress the point that migraine is to be considered when no other definite cause is found, especially if gastro-intestinal symptoms are present.

Headaches are divided into two major groups: the allergic or true migraine, and the non-allergic type.

The allergic headache is said to follow exposure to allergen(s), is often unilateral, may show cortical or sensory disturbances frequently of the visceral type, and usually end with nausea and/or vomiting.

The differential diagnosis is made by thorough study, including laboratory tests, basal metabolic rate, X-ray. Much emphasis is laid on exhaustive tests for sensitization to allergens.

After all studies and tests have been completed and correlated; the patient is instructed how to eliminate or avoid any foreign protein to which he is sensitive in order to lessen the allergic overload.

The authors present six cases which illustrate the effective control of migraine headaches by removal of allergens.—E. Sigmund LeWinn and B. B. Vincent Lyon.

SHACKMAN, R.

*"Jejunogastric Intussusception." British J. of Surg., 27:475, Jan., 1940.*

Jejunogastric intussusception is a rare complication of gastro-enterostomy. Three types are described; in type one the afferent loop passed into the stomach, in type two the efferent loop, and in type three both the afferent and efferent loops are involved.

The condition should be considered whenever a patient has abdominal pain and vomiting, with or without hematemesis, coming on any time after gastro-enterostomy. The etiology of the condition is obscure, but the treatment is surgical. In types two and three there is a 50 per cent mortality if operation is delayed more than forty-eight hours after the onset of symptoms.—C. Wilmer Wirts, Jr. and B. B. Vincent Lyon.

MOORE, THOMAS.

*"Simple Non-specific Ulcer of the Ascending Colon." British J. of Surg., 27:600, Jan., 1940.*

The history is reported of a patient who was perfectly well until the day before admission to the hospital when he suffered two attacks of pain in the right iliac fossa. The first attack lasted only a few minutes but the second forced him to stop working. He had no back pain, nausea, vomiting, urinary symptoms, or alteration from a normal bowel habit.

At operation a portion of the ileum, the ascending colon and a portion of the transverse colon was resected. The appendix was normal, but just above the ileo-cecal valve a small punched-out ulcer, 3 mm. in diameter, was seen. The ulcer extended through the bowel wall and communicated with a tiny cavity, the walls of which were formed by thickened peri-colic tissue.

The author believes that the primary change was a vascular one which led to necrosis of the bowel wall.—C. Wilmer Wirts, Jr. and B. B. Vincent Lyon.

WHEELER, SIR W. I. DECOURCY.

*"An Unusual Case of Obstruction to the Common Bile-Duct. (Cholechocele?)" British J. of Surg., 27:446, Jan., 1940.*

A report is made of a patient who was operated upon after several attacks of biliary colic and jaundice. The common duct was dilated but no cause for obstruction was found. At a second operation, sometime later, the common

duct was still greatly dilated but this time, upon opening the duodenum a cherry-sized cyst was found to be obstructing the orifice of the common-duct.

The author puts forth the theory that the mechanism of this condition is similar to a ureterocele. He suggests that in some patients the persistence of pain and jaundice after operation may be due to this cause, and not the result of an elusive stone, and therefore, in all obscure cases of biliary obstruction in the presence of a dilated bile-duct, search should not be abandoned until the duodenum has been opened and explored.—C. Wilmer Wirts, Jr. and B. B. Vincent Lyon.

REINHART, HARRY L. AND WILSON, SLOAN J.

*Malabsorption of Fat (Intestinal Lipodystrophy of Whipple). Report of a case. Am. J. Path., 15(4):483-491, 2 pl., 1939.*

A survey of the literature reveals 5 somewhat analogous cases, this case report constituting a 7th. The study of lipid metabolism in conjunction with a review of these cases suggests that this condition represents a massive excretion of fat, with an increased reabsorption of fat rather than a fundamental defect in the absorption of fat by the intestinal mucosa, and that the broad term "Intestinal Lipodystrophy" is most appropriate in our present state of knowledge of this disease.—H. L. Reinhart (Courtesy of Biol. Abst.).

REYNOLDS, LAWRENCE, MACY, ICIE G. AND SOUDERS, HELEN J.

*The Gastro-Intestinal Response of Children to Test Meals of Barium and Pasteurized, Evaporated and Base-exchanged Milks. J. Pediatrics, 15(1):1-12, 1 fig., 1939.*

7 healthy children, aged 7 to 11 years, whose gastrointestinal motility patterns were known served as subjects of serial roentgenographic studies upon the orderly passage through the alimentary tract of test meals composed of 2 ounces of BaSO<sub>4</sub> and 4 ounces of pasteurized milk, evaporated milk diluted 1:1 with water, and base-exchanged milk. Roentgen examinations were made at frequent intervals until the meal had passed out of the stomach and at 24-, 48- and 72-hour intervals after its ingestion, a total of 181 exposures. The average gastric emptying times for the 7 children were 227, 214, 193 minutes, respectively, for pasteurized, evaporated (diluted 1:1), and base-exchanged milks. The roentgenograms taken 10 minutes after ingestion indicated that the soft curd milks (evaporated and base-exchanged) began emptying from the stomach in much less time than had reached the duodenum and in 4 of these had entered the jejunum after 10 minutes, while in only one exposure at the 10-minute interval had the pasteurized milk meal left the stomach. The fluffier, more evenly dispersed masses formed by the processed milks, presenting greater surface areas to the digestive juices in the small intestine, and the more orderly progression of these soft curd milks throughout the alimentary canal, are in accord with results of metabolic and clinical observations upon the nutritive advantages of different milks.—Auth. summ. (Courtesy of Biol. Abst.).

FELDMAN, L.

*Jaundice as an Early Finding in Coronary Occlusion. Medical Clinics of North America, 24:263, No. 1, Jan., 1940.*

The author presents and discusses quite adequately a case of coronary occlusion in which jaundice appeared as an early symptom. He quotes from the literature that jaundice occurring as a late symptom in coronary occlusion is not uncommon. He presents the case as a differential diagnostic problem as to whether it represented primary biliary disease with reflex cardiac symptoms; or primary occlusion of the right coronary artery with prompt enlargement of the liver, associated with early

jaundice presumably due to anoxemia of liver cells; or a coincidental combination of both diseases.

After emphasizing that this male patient of 42 in his past history denied any previous complaints referable to either the cardiac or gastro-intestinal systems, the author proceeds to unravel the diagnostic problem in a satisfactory manner.—B. B. Vincent Lyon.

MURTAGH, JOHN A. AND TYSON, M. DAWSON.

*Esophagobronchial Fistula: A Result of a Foreign Body. New England J. of Med., 194, March 21, 1940.*

A single case is reported in which a rare type of fistula resulted from the lodgment of a bone in the esophagus with subsequent penetration into the left main bronchus. Two X-ray examinations and one esophagoscopy were negative. Because of the patient's condition, a gastrotomy was necessary. Following this, the patient developed broncho pneumonia. After recovery of this infection, the instillation of iodized oil into the trachea revealed a communication between the esophagus and the left main bronchus. Another esophagoscopy at this time was done and a foreign body protruding from the esophageal wall was removed. This was followed by a rapid convalescence and closure of the fistula.

The case is reported with the idea in mind that negative X-rays should not lead one to erroneously conclude that a foreign body is not present.—Henry H. Lerner.

HENRY, C. K. P.

*Extrahepatic Tumors of the Biliary Tract. Can. Med. Assoc. J., 42:251, March, 1940.*

From 1929 to 1938 inclusive at the Central Division of the Montreal General Hospital, the author reports 60 cases of extrahepatic tumors of the biliary tract. The group comprises benign and malignant tumors of the gall bladder and extrahepatic bile ducts. Among the latter is included a group of pancreatic malignancies involving the common bile duct. Unfortunately, the author has not segregated his cases so as to permit the reader to evaluate either the types or results of therapy. No cures of carcinoma of the gall bladder were reported, and the author states that he has never seen a carcinoma of the gall bladder that was removable at the time of operation.—Thomas A. Johnson.

WEBER, H. M. AND GOOD, C. A., Jr.

*Invaginated Appendiceal Stumps Roentgenologically Simulating Polypoid Neoplasms. Radiology, 34:440, April, 1940.*

The authors stated that there are no well defined criteria by which the distinction between the filling defect caused by invaginated appendiceal stump and that caused by a small polypoid neoplasm can be made. They presented four cases in which a preoperative roentgenologic diagnosis of a polypoid lesion was made, but histologic examination of the excised specimens disclosed inverted stumps of the vermiform appendix. They also encountered four similar cases where operation was deferred because the symptoms did not warrant operative interference. Weber and Good also called attention to the fact that they had observed benign and malignant polypoid lesions at the tip of the cecum in other patients.—Robert Turell.

YOSHII, NAOSABURO.

*On the Heat Production of Pancreas. III. On the Inhibitory Effect of Saline Solution on the HCl-Pancreatic Secretion. Jap. J. Med. Sci. III. Biophysics, 4(4):409-20, 1938.*

In dogs anesthetized with chloralose, intraven. inj. of isotonic saline, or intraven. or intraduodenal inj. of hypertonic saline was followed by a reduction in the amount of pancreatic juice secreted in response to a standard stimulus (inj. of 20 cc. 0.4 per cent HCl at body temperature into the duodenum via the choledochus); there was no effect on blood pressure or pancreatic temperature. Inj. of

defibrinated blood resulted in a response somewhat slower and somewhat less (in amount of juice secreted) as compared with the expts. with saline. Inj. of saline had no effect on the production of pancreatic juice in response to the intravenous inj. of secretin.—B. S. Walker (Courtesy of Biol. Abst.).

VERTUE, H. ST. H.

*Eumydrine in Pyloric Stenosis. Arch. Dis. Childhood [London] 14(78):173-179, 1939.*

This is a report of the use of eumydrine (atropine methyl nitrate) in 21 cases of pyloric stenosis. The drug was uniformly successful, as vomiting was usually stopped within 7 days, and weight regained within 8 days. The action of the drug is believed to cause relaxation of the pylorus and gastric musculature.—D. J. Pachman (Courtesy of Biol. Abst.).

BACON, HARRY E.

*Multiple Malignant Tumors, with Involvement of the Lower Bowel. Report of Multiple Primary and Contact Growths. Am. J. Cancer, 35(2):243-257, 5 figs., 1939.*

The literature on the occurrence of multiple primary malignant lesions with involvement of the anus, rectum, or sigmoid (omitting malignant polyposis) was reviewed. 145 cases with one or more of multiple growths in this locality were reported. These include 27 instances of dual carcinomata and 5 instances of triple carcinomata confined to the anus, rectum and sigmoid colon. In a somewhat greater number other portions of the gastro-intestinal tract were involved and in a few instances growths were present in systems unrelated to the rectum and sigmoid. 7 additional cases were presented, and 3 others in which there was no absolute proof of a multicentric origin were reported as possible examples of "contact" cancer. Carcinoma and sarcoma in the same individual were prone to occur in systems unrelated to each other. Malignancy, excluding cancerous alteration in intestinal polyposis, may be multicentric in origin; further, that this is by no means a rarity; in cases where 2 or 3 malignant and apparently primary growths are confined to a relatively small segment of bowel, approximately the same size and showing the same histologic characteristics as well as grade, multicentric origin may be, and often is, extremely difficult to determine.—Auth. summ. (Courtesy of Biol. Abst.).

CLAUSEN, JOHS., OG. RINGSTED, AXEL.

*Om prac- og Postoperative Vaeskebehandling hos Pylorostenotikere. [Pre- and Postoperative Fluid Treatment in Pyloric Obstruction]. Nordisk Med., 2(22):1649-1660, 10 figs., 1939.*

In patients with pyloric obstruction, dehydration and chlorine loss reach very low values (serum chlorine 170 mg. per cent), without it being possible, by the clinical examination alone, to estimate the degree of dehydration with accuracy. Dehydration and chloropenia may cause a lowering of the kidney function (in 1 case 5 per cent of the normal capacity). Adm. of a considerable amount of NaCl and fluid is frequently required for complete rehydration. The isolated examination of either diuresis, serum chlorine or urine chlorine provides no safe criterion of the state of hydration. The simultaneous detn. of the serum chlorine conc. and the 24-hour urine chlorine conc. afford the best indication of the degree of rehydration of the body. In patients highly undernourished and highly dehydrated due to the long continued obstruction, these detns. must be supplemented with analyses of the plasma protein to prevent the risk of development of a hypoproteinemic edema. In patients with hypoproteinemia, blood transfusion must be given in the pre-operative treatment in order to raise the serum protein conc. and render rehydration possible.—J. Bing (Courtesy of Biol. Abst.).

LYONS, RICHARD H. AND BRENNER, CHARLES.

*Erythropeiosis Following Bleeding Peptic Ulcer. Am. J. Med. Sci., 198(4):492-501, 1939.*

237 hospital records of bleeding peptic ulcer were analyzed with special reference to symptomatology anemia produced, and subsequent course. Symptoms of weakness, syncope or dyspnea preceded external evidence of bleeding in 1/3 of the cases. Symptoms of exacerbation of ulcer activity preceded bleeding in only 28 per cent. Severity of the hemorrhage was independent of age and sex. Previous duration of symptoms and number of previous hemorrhages were essentially independent of age. The rate of erythropeiosis once the lowest RBC count had been reached was strictly dependent on the degree of anemia at the moment regardless of the duration of the illness and the initial severity of the anemia. Patients treated on Sippy régime had as good erythropeiosis as was reported with the so-called "puréed diet." Transfusion did not affect erythropeiosis beyond the actual increment of donated cells. The net mortality was 5.5 per cent. This was independent of sex or number of previous hemorrhages.—Authors (Courtesy of Biol. Abst.).

MONAUNI, J.

*Studien über die Objektiven Faktoren des Hungers und des Sattseins. Wiener Arch. Inn. Med., 32(4):159-188, 1938.*

Blood-sugar detns. and X-ray records of the stomach were obtained upon subjects with normal digestive function and with specific digestive disorders at intervals of 30 minutes or less for 2½ hours after feeding a BaSO<sub>4</sub> test meal. The simultaneous effects of sugar, by ingestion, intraven. inj., intraduodenal inj. and intrajejunal inj., of sugar free foodstuffs and of insulin were studied. Ibid, 32(5):215-240, 1938. The data are discussed and various hypotheses are considered to explain hunger and satiety. The similarity of the effects of insulin injection to the objective signs of hunger (gastric activity, hypersecretion, and hypoglycemia), lead to the adrenalin-insulin hypothesis of hunger and satiety.—E. Mendelson (Courtesy of Biol. Abst.).

MAYO, CHARLES W. AND MILLER, JOSEPH M.

*Endometriosis of the Sigmoid, Rectosigmoid and Rectum. S. G. O., 70:2-136, Feb. 1, 1940.*

The purpose of this article is to describe endometrioma so as to distinguish it from carcinoma. Mayo and Miller define an endometrioma as "a tumor or tumors composed of aberrant endometrial cells associated with smooth muscle cells in some situations. It occurs in women between 30 and 49 years of age usually, and symptoms are usually present for a longer time than in inflammatory conditions or carcinoma. Periodic symptoms include constipation, dysmenorrhea, diarrhea, rectal bleeding and pain. Sterility and general discomfort in the lower portion of the abdomen are often associated with this disease.

Statistics and symptoms of 38 cases encountered at the Mayo Clinic are discussed. It was found that an accurate, detailed history and inspection and palpation of the pelvic region are important in diagnosing endometriosis.

The best treatment is conservative resection of the bowel since this will allow the patient to have children. This procedure is especially good if the lesion is malignant, if metastasis is not found and if evidence of endometriosis is absent in the pelvis. If the patient is near the menopause age, the more radical treatment of radium implantations or roentgen-ray is employed because it usually offers the possibility of the induction of an artificial menopause and at the same time corrects the endometrioma. If there is an obstruction, a temporary colonic stoma may be made and then radical therapy used.—Francis D. Murphy.

CUNHA, FELIX.

*Appendicular Pylephlebitis. J. Int. College of Surgeons, Vol. III, No. 1, p. 18, Feb., 1940.*

Pylephlebitis, the term used to indicate thrombophlebitis of the portal vein or portal system, is most commonly associated with acute appendicitis and is frequently a post-operative complication. Forty-eight or seventy-two hours following appendectomy, or even later, there occurs a chill or chills with a rapid rise in temperature to about 104 degrees. The temperature then takes on the typical septic curve, down in the

morning, up in the afternoon, with or without the recurrence of chills. The patient begins to present definite evidence of septic infection in his face and skin and by pulse elevation and respiratory increase, although the abdomen, particularly the right lower quadrant, may be soft and entirely free of spasm or rigidity of the musculature. Nevertheless, the patient has definitely the appearance of serious illness. If the process is to extend along the portal system and involve the liver, there will appear a gradually increasing jaundice, with some tenderness and soreness over the

liver area. An enlarged palpable liver may or may not be present, depending entirely upon the size and location of the abscess formation in the liver.

Ligation of the ileocolic vein is useful if carried out preoperatively. It is recommended as a prophylactic in cases in which there is much congestion and engorgement, extensive edema or cellular infiltration of the retrocecal structures, or in which the appendix is greenish and reddened, with gangrene or abscess formation.

Franz J. Lust.

JOHNSTON, CHARLES G.

*Decompression in the Treatment of Intestinal Obstruction. S. G. and O., 70:2A-365, Feb. 15, 1940.*

In cases of simple acute obstruction, enterostomy is a successful method of decompression of the distended bowel and relieves the obstruction. However, it does not get at the cause of the obstruction and may only offer temporary relief.

The more modern method of decompression is by means of intubation. The tubes are usually introduced into the intestinal tract through the natural orifices and are about 10 feet long with an inflatable balloon at the lower end. The balloon is inflated and peristalsis propels the tube downward until stopped by obstruction to its passage. Usually a large tube is used for aspiration and a smaller tube for inflation of the balloon. Intestinal intubation helps determine the type, extent and level of the obstructing lesion, and if the tube is passed well down in the intestine, the patient may be fed a diet low in fiber content and absorption of food, fluid and salt occurs.

This method relieves the patient's distention without operation and makes it possible to delay surgery until the patient has a normal fluid and chemical balance and the difficulties encountered of operation amid distended loops is removed. The obstruction can be localized before operation through the use of small amounts of barium given through the tube for roentgenographic studies. In the treatment of adynamic ileus, there seems to be enough muscular power left in the intestinal wall to pass the tube down once the over-distention is relieved. If there is a definite organic lesion, operation is still necessary but it is much easier for both the surgeon and patient.

Certain disadvantages are connected with this procedure. There is the possibility of failure to recognize interference with the mesenteric blood supply though this recognition is not difficult to make. Difficulty is encountered in introducing the tube into the duodenum and intubation of the small intestine is thus hard work and requires constant care. Sometimes the tube causes irritation to the nose and

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## Studies on the Effect of Human Gastric Juice on the Reticulocytes of Albino Rats\*

By

CARL P. SCHLICKE, M.D.†  
ROCHESTER, MINNESOTA

THE need for a laboratory test for the identification of factors that prevent pernicious anemia and for a non-clinical method of assay for preparations that prevent pernicious anemia is recognized by all who have had any interest in the disease. Work in this direction has been handicapped by the absence, in species other than man, of a condition comparable to pernicious anemia. Investigations accordingly have been limited to a study of the effects of the materials in question on normal animals or on animals with artificially produced anemias, and to biochemical tests.

Investigations conducted on normal animals have been concerned chiefly with observations of the fluctuation which could be produced in the number of circulating reticulocytes by the administration of anti-anemic preparations. It was known that in patients with pernicious anemia, the first evidence of response of the bone marrow to an effective hemopoietic stimulus was the appearance of immature cells in the peripheral blood. The reticulocytosis, which was the result of the development of primitive cells in the marrow, varied inversely with the level of the hemoglobin and erythrocytes before treatment. The initial increase in the erythrocyte level in severe cases was largely due to the increased number of reticulocytes. Between certain maximal and minimal amounts, the reticulocyte increase in severe cases was proportional to the quantity of active principle administered. The failure to obtain a reticulocyte response in a patient with an initial erythrocyte count less than 3,000,000 per cubic millimeter of blood indicated either an impotent medication or an incorrect diagnosis. Since this reaction was so characteristic in man, and so useful in testing the potency of therapeutic agents, as long as the possibility of nonspecific reactions (especially after parenteral treatment) was kept in mind (Minot and his associates (1, 2)), many investigations were carried out in the effort to demonstrate a similar reaction in animals, in spite of the fact that in man these responses occur only in cases of pernicious anemia and not in normal individuals.

The first work of this type was carried out on pigeons by Vaughan, Muller and Zetzel (3), who in 1930 described an increase in the number of circulating reticulocytes after the intravenous injection of liver extract. Guinea-pigs were utilized by Jacobson (4) in his extensive studies, the first reports of which appeared in 1934. Dogs, rabbits, sheep and pigs have also been used. In spite of occasional satisfactory reports, most workers have found difficulty in obtaining consistent, satisfactory and dependable results with any of the animals tested.

Perhaps the most widely studied animal has been the rat. Vaughan and Muller (5) in 1932 found liver and liver extracts without effect on the body weight, red cells and reticulocytes of normal adult male rats. In this same year, however, Gebhardt and Cario (6) stated that daily injections of 2 cc. of normal gastric juice into old male rats produced an increase in the number of circulating reticulocytes on the fourth or fifth day after the initial injection. This work led Singer (7) to carry out the investigation which culminated in the development of the "rat-reticulocyte-reaction" test which bears his name.

Singer used white rats weighing 150 to 200 gm. which he kept on a bread and milk diet as he felt this favored a stable reticulocyte level. Reticulocytes were counted in fresh preparations of blood obtained from the tail. Counts were made on two days preceding the test for control purposes. The rats then received a single injection of 2 to 20 cc. of human gastric juice neutralized with sodium bicarbonate. A "positive" response began on the second day, reached its peak on the third and subsided to normal by the sixth day. The height of the response was independent of the amount of gastric juice injected. Singer gave the normal reticulocyte range as 0 to 1.4 per cent. When normal gastric juice was injected, reticulocyte values between 1.7 and 3.4 per cent were observed. Gastric juice from patients with simple achlorhydria or with hemolytic icterus gave a similar response, but uniformly "negative" results followed the use of gastric juice from patients with pernicious anemia. The reticulocytogenic property of normal gastric juice could be destroyed by heating. A neutralized mixture of hydrochloric acid and pepsin did not produce a response. Singer concluded that the presence or absence of "Castle's (8, 9) principle" in any given specimen of gastric juice could be determined readily by injecting 2 or 3 cc. into one rat and 5 to 8 cc. into another and observing the reticulocyte level.

The importance of this work led to widespread attempts at confirmation. Numerous workers now accept the test as reliable. Rauschenberg (10), Hitzenger (11) and Fejgin and Ptonskier (12) were early impressed with its value. Baráth and Fülöp (13) described reticulocyte levels of 18 to 20 per cent after the injection of gastric juice from patients with polycythemia vera. Crosetti, Bajardi and Margulius (14) confirmed Singer's observation but reported a return of the reticulocytogenic agent to the gastric juice of pernicious anemia patients during spontaneous or liver induced remissions. Salah (15) used the method to demonstrate the presence of hemopoietic material in the achlorhydric gastric juice of pellagrins. Kinkel-Diercks and Kinkel (16) reported "negative" rat re-

\*This work was done in the Division of Experimental Medicine, The Mayo Foundation.  
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ticulocyte responses in premature infants, the reticulocytogenic power appearing during the first few years of extra-uterine life. This power was present at birth in the gastric juice of full-term infants. Storti and Rettanni (17) concluded that the reticulocytogenic agent and Castle's principle were identical or at least that there was a direct parallelism between their presence in gastric juice.

Leiner (18) and later Singer and Wechsler (19) described positive "rat-reticulocyte reactions" when the urine from normal individuals was injected, while the urine from patients with pernicious anemia gave negative results. Since heating did not destroy the reticulocytogenic power of normal urine, and since this power was also inherent in the urine of adequately treated patients with pernicious anemia, it was postulated that the finished antianemic principle and not the "intrinsic factor" was responsible for the positive urine reactions.

The reports of other workers are less conclusive. Kamerling (20) obtained a "positive R. R. R." with normal gastric juice but was unable to obtain it if peptic activity was destroyed by heating or neutralization before injection. Moreover he obtained positive reactions with mixtures of pepsin and hydrochloric acid, as did Fleischhacker and Schlesinger (21). These latter authors also obtained positive responses with one-third of the specimens of gastric juice from patients with pernicious anemia and negative results with gastric juice from patients with polycythemia vera. Sala (22) extracted the liver of a patient who had died from pernicious anemia and prepared digests of the gastric mucosa. The liver preparation produced a reticulocyte response in rats but the gastric preparation did not. He found further that the liver preparation produced a reticulocyte response when administered to a patient with pernicious anemia, but did not otherwise alter the blood picture. He concluded that the reticulocyte response was not dependent on the antianemic principle. Klaperszak (23) shared this opinion. He concluded that the rat reticulocyte response was a protein reaction as it did not appear after the injection of deproteinized gastric juice.

Engberding (24) concluded that the rat was not a suitable animal for testing for the presence of anti-anemic material in gastric juice, since in his experiments he was unable to distinguish between the reticulocytosis resulting from an injection and that resulting from loss of hemoglobin due to repeated blood sampling. Plaut (25) stated that the rat reticulocyte reaction could not be due to the "intrinsic factor" as she obtained positive responses with heated as well as unheated gastric juice obtained from normal individuals and from patients with pernicious anemia. Other unfavorable reports have come from Jesquier and Apsey (26), from Dreher (27) and from Creskoff and Fitz-Hugh (28). The last mentioned workers found that "therapeutically inert materials (e.g. dilute hydrochloric acid) and indeed administration of no material (control rats) may evoke reticulocyte rises of far greater magnitude than those regarded as significant by Singer."

During recent investigations on the effects of orally administered human gastric juice on the blood of female albino rats and their offspring it was felt that it would be of interest to observe the effects of these administrations on the reticulocyte levels of adult

male rats. Methods and findings are herewith presented. The author wishes to express his appreciation to Dr. G. M. Higgins for his generous aid in the carrying out of this study and to Miss Catherine Sawyer for her assistance in securing specimens of gastric juice.

## METHODS

A number of male albino rats on an adequate stock diet were subjected to daily reticulocyte counts. For this purpose a drop of blood was removed from an ear vein, mixed with a small amount of aqueous brilliant cresyl blue, spread out on a clean glass slide, and counterstained with Wright's stain after drying. The percentage of reticulated cells encountered while counting 500 to 1000 erythrocytes was recorded. As a control, the effects of daily blood sampling on the reticulocyte level of nine untreated rats were noted over a period of ten days.

Nine male rats received a single dose of 6 cc. of normal human gastric\* juice by intubation. This amount almost equals the capacity of the rat's stomach. Nine male rats were similarly treated with 6 cc. of normal gastric juice which had been heated over a boiling water bath for twenty minutes. After seven days this group of rats received 6 cc. of gastric juice neutralized with sodium hydroxide. Nine male rats were given 2 cc. of a preparation of liver extract (Valentine's) known to be effective when administered orally in the treatment of pernicious anemia. In each of the foregoing experiments the test material was administered by gastric intubation.

Neutralized normal human gastric juice was injected intramuscularly into nine male rats. One of these rats received 3 cc., seven rats each received 5 cc. and one rat received 8 cc. Five cubic centimeters of heated normal gastric juice was injected intramuscularly into each of four male rats.

In each case, control periods of two to six days, during which daily reticulocyte counts were taken, preceded the administration of the various test doses. Only one dose was administered to each animal for any given test, but in some cases, after an interval of several weeks, animals which had previously been tested were used again. During all observation periods following the various type of treatment the reticulocyte levels of four to seven untreated animals were followed for purposes of control.

In order to comply more closely with the directions given for the Singer test, nine rats were placed on a bread and milk diet. After intervals of six weeks to six months these animals were subjected to tests similar to those performed with the animals on a stock diet. Because of the limited number of animals in this group, the same animal was often subjected to several tests, an interval of several weeks being allowed to elapse between tests. Seven of the "bread and milk" rats each received a single dose of 5 cc. of neutralized normal gastric juice by intubation and subsequently a 3 cc. dose of the liver extract already described. Seven animals each were given 5 cc. of neutralized normal gastric juice by intramuscular injection. Two rats each received injections of 5 cc. of neutralized normal gastric juice which had been reduced from 50 cc. by distillation *in vacuo*. Four rats each received 5 cc. of heated normal gastric juice by

\*All gastric juice was obtained from the gastro-enterologic laboratory, where samples are taken following ingestion of a test meal of arrowroot biscuits and water.

intramuscular injection. Two rats each received injections of 5 cc. of heated gastric juice which had been reduced from 50 cc. by distillation in vacuo.

## RESULTS

1. *Rats on stock diet.*—a. Effect of daily blood sampling.—The initial range of reticulocyte percentages in this group of animals was 0.6 per cent to 3.2 per cent with a mean of 1.4 per cent. During the first four days of observation the levels ranged between 0.2 per cent and 3.4 per cent. On the fifth day one animal had a reticulocyte count of 4.8 per cent. Between the sixth and tenth days, three animals had counts exceeding 5 per cent (the highest 7.2 per cent) while the other six animals showed no significant deviation from their normal level. In all experiments, the mean reticulocyte level was found to be higher in animals subjected to daily blood sampling than in those from which blood was being taken for the first time. It was also found that animals that became ill or in which diarrhea developed showed elevated reticulocyte counts. In female rats, pregnancy is associated with slight reticulocytosis.

b. The effect of orally administered, normal human gastric juice.—Five of the animals in this group showed no significant change in their reticulocyte level after the intubation. In one animal the reticulocyte level rose to 23.6 per cent on the third day and did not return to normal throughout the experiment. The reticulocyte levels of the remaining three animals rose gradually to peaks of 6 per cent to 11 per cent on the third or fourth day and then returned gradually to normal. The levels of three of the untreated controls climbed to 5.2 per cent to 7.0 per cent during the experiment, and the curves of these values except for their slightly lower peaks did not differ from those of the treated animals.

c. The effect of orally administered, heated normal human gastric juice.—The reticulocyte values of this group of animals remained on the whole quite level. Isolated counts of 4 per cent to 6 per cent were noted but the general tendency was toward a fairly low, stable level, not unlike that of the untreated controls.

d. The effect of orally administered, neutralized normal human gastric juice.—Three of the animals in this group which had been having values of 0.6 per cent to 2.6 per cent showed a gradual rise to a peak of 3.6 per cent to 3.8 per cent on the third or fourth day after intubation. The remaining six animals showed no significant fluctuation in their reticulocyte levels, although counts of 4.0 per cent to 5.4 per cent were noted in animals which habitually had high counts.

e. The effect of orally administered liver extract.—None of the animals in this group showed increases in the number of circulating reticulocytes which could be attributed to the material administered, although in three of the animals peaks of 5.2 per cent to 9.6 per cent were reached on the fifth or sixth day. The reason for discrediting these apparent "responses" was the behavior of the control group. The six untreated animals showed consistently low values throughout the control period, but during the test period (although they received none of the material given to the test animals), a number of them exhibited gradual reticulocyte increases to levels of 8 per cent and 11 per cent, followed by gradual decreases to normal levels,

which could in no way be distinguished from the changes occurring in the test animals.

f. The effect of the intramuscular injection of neutralized normal human gastric juice.—Two of the animals which received 5 cc. doses showed reticulocyte levels of 5.2 per cent and 6.8 per cent on the tenth and eleventh days respectively. The other five each receiving 5 cc. and the two receiving 3 cc. and 8 cc. showed no significant reticulocyte responses. Peaks of 4.8 per cent and 5.8 per cent were reached on the ninth day by two of the control animals into which heated juice was injected.

2. *Rats on bread and milk diet.*—a. Effects attributable to deficient diet.—Although a diet of white bread and milk does not represent a complete well-balanced diet and is quite deficient in iron, none of the rats on this diet became anemic. The blood values of the rats that had eaten nothing else for six months were essentially the same as at the beginning of the experiment. Moreover, the change from a stock diet to a bread and milk diet did not result in an alteration of the reticulocyte level. An increased tendency toward the maintenance of low and stable reticulocyte values was not noted in the animals on this diet.

b. The effects of orally administered, neutralized normal human gastric juice.—There was no significant alteration in the reticulocyte level of any of the animals on a bread and milk diet following intubation with 5 cc. of neutralized normal gastric juice.

c. The effect of orally administered liver extract.—Orally administered liver extract in doses of 3 cc. was without effect on the reticulocyte level of the rats on a bread and milk diet.

d. The effect of the intramuscular injection of neutralized normal human gastric juice.—There were no variations in the reticulocyte level of rats on a bread and milk diet following the injection of neutralized normal gastric juice which exceeded or could be differentiated from those which occurred in untreated controls or animals which received gastric juice which was heated before administration. The mean reticulocyte counts on the ninth and tenth days after injection seemed to be slightly higher than at any other time following injection. This was found to be the case also in those animals that received concentrated gastric juice whether this was heated or not. Two of the animals that received the concentrated gastric juice died within twenty-four hours after its injection. In the two that survived sloughs developed at the site of injection at the end of one week. This makes one suspect that the irritation and tissue damage produced by injection may have been responsible for the delayed slight mean increase in the number of circulating reticulocytes in these cases.

## COMMENT

The results of these studies have been in general disappointing. Occasionally responses occurred, after the administration of materials containing antianemic substances, which were quite suggestive but they were not consistent. It was found impossible to secure a group of rats, even with the use of a bread and milk diet, which showed no spontaneous fluctuations in the reticulocyte level. Numerous rats were found which would have values of less than 1.5 per cent for a week or more, but unpredictable rises were the rule when the animals were followed for any length of time.

These rises could in no way be distinguished from those thought to be due to substances administered. Repeated blood sampling may have played a role in their production.

The great significance which some investigators have attached to minute fluctuations in the reticulocyte level, even could they be detected by ordinary methods of enumeration, would be of value only in rats which could be depended on to have habitually low counts. Unfortunately, the rats used in this study did not display any such praiseworthy stability. The association of an elevated reticulocyte count with infections, with diarrhea and, in female rats, with pregnancy, served to emphasize the nonspecific character of the reaction.

By more careful selection of animals from a much larger series of rats than was here employed, a group suitable for the reticulocyte test might possibly be found. But in the stock laboratory rat, living under fairly standard conditions, the reticulocyte response is

not a suitable criterion for utilization in the detection of antianemic factors or in the determination of the potency of materials known to contain such factors.

### SUMMARY

Normal human gastric juice, heated normal gastric juice and neutralized normal gastric juice have been administered to adult male rats by gastric intubation, without producing any consistent or predictable changes in the number of circulating reticulocytes. Intramuscular injections of gastric juice and gastric juice concentrates did not produce reticulocyte responses which could not be ascribed to irritation and tissue destruction. The nonspecific character of reticulocyte responses in the rat has been emphasized and the normal lability of the reticulocyte level pointed out. The reticulocyte response in rats has not proved in our hands a reliable method for detecting the presence of antianemic substances.

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## The Effect of Long-Continued Ingestion of Oxidized Bile Acids on the Dog and Rat\*

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**I**n a recent article Schmidt, Beazell, Atkinson and Ivy (1) observed that oxidized unconjugated bile acids, in large doses, 5 gm. daily, depressed natural cholic acid synthesis, at least in some dogs. These

authors asked the question, "Is this a manifestation of toxic effects on the hepatic epithelium?" In a recent investigation (2), we have found that the oxidized unconjugated bile acids do not uniformly depress cholic acid synthesis even in 5 gm. daily doses. Yet, they cause a marked hydrocholerisis and are handled differently in the body from the salts of taurocholic and

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glycocholic acids. Does the hydrocholeresis induced by the oxidized bile acids indicate hepatic irritation? Does the small recovery and delayed excretion of the oxidized bile acids (2) in the bile have any toxicological significance?

It seemed that if the oxidized bile acids did irritate or effect the liver toxicologically, their long-continued ingestion should produce changes in the liver. Accordingly we have studied the effect of the oxidized bile acids given in relatively large daily doses on the histology, glycogen and fat content of the liver in dogs and rats. In addition the bromsulphalein clearance of the dogs was determined at various intervals.

#### METHOD

Six normal dogs, weighing approximately 10 kilos, were placed on a standard diet of corn meal mush, meat and bones. One dog was fed 3 grams of ketocholic acids (Ketochol) per day. Two dogs were fed 3 grams of dehydrocholic acid (Decholin) each day. Two dogs were fed 3 grams of oxidized conjugated hog bile salts (Dechacid No. 22), and one was fed 3 grams oxidized conjugated ox-bile salts (Dechacid No. 14) each day. The dogs were weighed about every two weeks and evidence of diarrhea was looked for. The bromsulphalein dye excretion test, according to the method of Dragstedt (3), was used as an estimate of liver function. Five mgs. per kilo of the dye were injected intravenously, and blood samples were drawn 5 and 20 minutes later, and the dye concentration in the plasma determined. The oxidized bile salts were fed for at least 3 months. At the end of that time the bromsulphalein test was repeated and the dogs sacrificed. Sections of the liver and kidney were removed for histologic studies. The remaining liver tissue was ground and an aliquot removed for total lipid analysis. The total liver fat method of Best (4) was used.

Similar experiments were made on two groups of white male rats. These rats weighed between 200-350 grams and were approximately 60-100 days of age. The first group consisting of 40 animals was divided into 4 sections; one consisting of 10 control animals, while the three other groups of 10 animals each were given 0.3 gm. per kilo of Ketochol, Decholin and Dechacid No. 14 respectively. These oxidized bile salts were suspended in water and injected subcutaneously. The control animals received similar doses of physiologic saline subcutaneously. Daily injections were maintained for at least 30 days. Numerous subcutaneous injections of oxidized ox-bile salt (Dechacid

No. 14) resulted in multiple skin abscesses, which also occurred, but to a lesser extent, in the Ketochol-treated animals. Abscesses did not occur in the rats injected with Decholin. At the end of the feeding period the rats were starved for 48 hours. The animals were then sacrificed and the livers removed, weighed, ground up, and an aliquot removed for total fat determination.

Another group of 60 rats was divided into 4 groups. One group of 20 rats served as the control, while the remaining animals were divided into equal groups and given doses of 0.3 gm. per kilo Ketochol, Decholin and Dechacid No. 14, as above. To obviate the objections to the subcutaneous route, the oxidized bile salts were suspended in a thick sucrose mixture and fed orally by means of a tuberculin syringe. The control animals were fed the sucrose solution. Each group of treated animals was fed their respective oxidized bile salt for at least one month and then sacrificed along with a certain number of control animals. The rats were starved for 48 hours and then allowed to eat during the last 12 hours. The Dechacid No. 14-treated rats were allowed to eat only during the last 6 hours. Then each rat was anesthetized with an intraperitoneal injection of nembutal (sodium pentobarbital). The abdomen was opened, and the liver frozen *in situ* with liquid nitrogen. The frozen liver was then removed and powdered so that the entire liver could be analyzed for glycogen content according to the method of Somogyi (5).

To complete the study six normal dogs were placed on a standard diet of corn meal mush, meat and bones, and fed 5 grams of oxidized bile salts per day for from 3 to 7 months. The animals were divided into 3 pairs, and one pair was fed 5 grams Decholin per day, while the other two pairs of dogs were fed similar doses of Dechacid No. 14, and Ketochol, respectively. Care was taken to observe their diet, appetites, weights, signs of diarrhea, and at the same time numerous bromsulphalein excretion tests were made as an estimate of liver function. At the end of 3 to 7 months the dogs were sacrificed. The animals were anesthetized with nembutal and the abdomen was opened widely so as to have free access to the entire liver. A few small sections of the liver were removed for histologic study, and then the liver was removed in one piece and immediately immersed into a liter of liquid nitrogen, thus freezing the liver. Approximately one minute elapsed between the time the animal was

TABLE I  
*Effect of long-continued feedings of 3 grams of oxidized bile salts per day in normal dogs*

Dog	Regime 3 Grams/24 Hours	Weight—Kilos		Total Days	% Retention of Bromsul. Dye at 20 Min.	% of Total Liver Lipids
		Before	After			
1. Female	Ketochol (ketocholic acid)	8.0	8.6	90	0	6.4
2. Female	Dechacid No. 22 (oxidized hog-bile salts)	11.4	11.5	90	0	6.2
3. Female	Dechacid No. 22 (oxidized hog-bile salts)	7.7	8.4	90	0	5.8
4. Female	Decholin (dehydrocholic acid)	12.0	12.0	90	0	6.4
5. Male	Decholin (dehydrocholic acid)	12.4	12.5	90	0	6.3
6. Female	Dechacid No. 14 (oxidized ox-bile salts)	7.5	8.5	104	0	4.9

TABLE II

*Effect of subcutaneous injections of 0.3 gm./kilo per day of oxidized bile salts in white rats*

Regime	No. of Rats	Dose Per Day	Days	Av. Wt.—Grams		Av. Wt. of Liver (wet)	Percentage of Total Liver Lipid Av.
				Before	After		
Ketchol (ketocholeic acid)	9	0.3 gms./kilo	31				4.82 ± 0.7
Decholin (dehydrocholic acid)	8	0.3 gms./kilo	39	225	185	6.030	5.7 ± 0.6
Dechacid No. 14 (oxidized ox-bile salts)	5	0.3 gms./kilo	29	225	221	6.821	3.2 ± 0.6
Control	7	0.3 gms./kilo (NaCl)	39	325	234	3.872	6.1 ± 0.5
				175	228	6.867	

anesthetized and the liver frozen, and large aliquots were taken for liver glycogen and total fat analyses.

## RESULTS

Table I gives the results which were obtained when dogs were fed 3 grams of various oxidized bile salts for at least 90 days. In all cases the animals maintained their pre-experimental weights or else showed a gain in weight. When 5 mgms. per kilo of bromsulphalein dye were injected intravenously, no dye could be found in the peripheral blood at 20 minutes. The percentage concentration of dye in the blood at 5 minutes varied between 15% and 25%. The total fat concentration of the livers ranged between 5% and 6%. Good checks were obtained in those instances where two dogs had been fed the same oxidized bile salt. Thus the Dechacid No. 22 (oxidized hog bile salts)-treated animals had a liver fat concentration of 6.2% and 5.8%, while the Decholin-(dehydrocholic acid) treated animals had a fat concentration of 6.4% and 6.3%.

Table II lists the results obtained on the subcutaneously-injected rats. There was a marked reduction in weight of the Ketchol and Dechacid No. 14-treated rats. Because of the slow absorption or local irritation of these preparations, abscesses formed at the sites of injection. Their appetites decreased with a resulting decrease in total body weight. Decholin, apparently quickly absorbed, did not cause abscesses, and consequently had no serious effect on the appetite of these animals. The weights of the Decholin-treated animals remained fairly constant. The average per cent of total liver fat in the controls was  $6.1 \pm 0.5$ . The treated animals had a liver fat concentration smaller than that of the controls (Table II). The total fat content of the liver of the Decholin and Ketchol-treated animals averaged  $5.7 \pm 0.6\%$  and  $4.8 \pm 0.7\%$ , respectively, while the Dechacid No. 14-treated had a low average concentration of  $3.2 \pm 0.5\%$ . In this latter

group the average weight of the liver was relatively low, only amounting to 3.872 grams, whereas the average weight of the liver in the other groups was above 6.0 grams.

The results on those rats which were fed the oxidized bile salts orally are shown in Table III. The weight of all the treated animals showed a 10-20% increase during the period of treatment. The liver glycogen of the control and the treated animals was determined and is indicated in the table as the per cent of the total weight of the liver. In all cases, the per cent of glycogen in the treated livers approximated that of the corresponding control group. When the total average per cent of glycogen in the treated animals, 4.4%, is compared with that of the control group, 4.9%, it is obvious that a significant difference between the two groups does not exist. The glycogen content of the liver of the Dechacid No. 14-rats as well as their control groups was less than that of the other groups because food was given to these rats for only 6 hours after a previous fast of 48 hours; the other animals were allowed food for 12 hours after their fasting period.

Table IV gives the results obtained when 5 grams of the oxidized bile preparations were fed orally to dogs. There were no weight losses and a few of the dogs gained weight. At 20 minutes no bromsulphalein could be detected in the peripheral blood, and the values at 5 minutes were normal. The average concentration of total liver fat in 6 dogs was 4.3 per cent, while the glycogen content was 5.6 per cent.

The histological sections of the dogs' livers were examined especially for increased fat deposition. No sections showed any signs of fatty infiltration or fatty degeneration. In a few instances there were some evidences of passive hyperemia and a small amount of round-cell infiltration, which is not infrequently found in the dogs' liver. The fibrous tissue was normal in

TABLE III

*Effects of oral feeding of 0.3 gm./kilo per day of oxidized bile salts to white rats*

Regime	Av. Percentage of Glycogen in Liver				Av. Wt.—Grams				Total Days
	Control		Treated		Control		Treated		
	No. Rats	%	No. Rats	%	Before	After	Before	After	
Ketochol (ketocholeonic acids)	7	6.6± 0.3	11	5.6± 1.6	216	236	242	262	38
Decholin (dehydrocholic acid)	6	5.1± 0.9	11	4.7± 0.3	224	252	204	255	32
Dechacid No. 14 (oxidized ox-bile salts)	7	3.1± 0.2	10	3.4± 0.4	227	270	231	261	36
Total averages	20	4.9	32	4.4	222	253	225	259	

distribution. The intra-hepatic bile ducts were not dilated or distended. In one dog, No. 4 (Table IV), the pre-treatment sections of the biopsy of the liver showed many areas of fatty infiltration of the liver cells. After four months of oxidized bile salt feeding, the liver specimens were normal and showed no areas of fat deposition. In the sections of the kidney no evidences of abnormality could be found.

### DISCUSSION

This study was undertaken to ascertain what toxic effects, if any, the oxidized bile acids have on the liver. It has been repeatedly observed that toxic substances or irritants, such as carbon tetrachloride, alcohol, chloroform, and phosphorous, when administered to experimental animals will produce a fatty liver. Accompanying this change there occurs a reduction in the glycogen content of the liver and a decrease in the functional activity of the liver. Further, the animals become listless and lose their appetites with a resulting decrease in body weight. If allowed to continue on the same regime the animals soon reach a state of inanition and die. No such picture was observed in our dogs. They all maintained their weights or else showed a gain. The rats that were fed the oxidized bile salts orally did not show any decrease in their weights. Only those rats that were injected subcutaneously with Dechacid No. 14 (oxidized ox-bile salts) and Ketochol (ketocholanic acids) lost weight. This apparently was due to the relatively slow absorption or local irritation of these oxidized bile salts which caused necrosis at the site of injection. Since Decholin (dehydrocholic acid) is claimed to have a low intravenous toxicity and appeared in our experiments to be absorbed rather rapidly from the subcutaneous tissues, the Decholin-treated rats showed no local ill-effects at the site of injection, and all of them maintained their weights. Although the present liver function tests do not indicate minor disturbances in the liver function, the normal results that we obtained with the bromsulphalein tests definitely indicated that there was no demonstrable reduction in the factor of safety of the liver.

Another method for determining whether these oxidized bile preparations have a "toxic" action on the liver consisted in analyzing the liver of our animals for total fat and glycogen content. Various workers in our laboratory, using the standard diet of corn meal mush, meat and bones, have found that the normal fat content of dog's liver ranges between 5 per cent and 6 per cent. Using this as our standard or normal value, we find that our range, 4 per cent to 6 per cent,

of total fat compares very favorably with their results. However these figures are somewhat higher than those reported in the literature, such as the maximum value of 3.4 per cent total fat obtained by Kaplan and Chalkoff (6). Nevertheless, it is obvious that whatever standard we use as our comparison, the values of 4 per cent to 6 per cent for total liver fat found in our experimental dogs does not indicate the presence of increased fat deposits in the livers. The fat content of fatty livers usually ranges from 10 per cent upwards, but in no case did our analyses reveal a fat concentration greater than 6.6 per cent. Similar negative results were obtained in our analyses of the rats' liver for total fat content. Table II shows that in all the treated animals the fat content of the liver was less than that of the controls, which averaged 6.1 per cent. This occurred in spite of the fact that a large number of the Dechacid No. 14 and Ketochol-treated rats showed a reduction in body weight, because of fasting, which usually increases the fat content of the liver. We do not wish to imply that oxidized bile salt feeding will prevent the formation of fatty livers, but it is obvious that the oxidized bile preparations used in our experiments did not increase the fat content of the liver.

Further, our results show that there was no decrease in the glycogen content when the liver of the dogs and rats was analyzed. All those investigators who have made liver glycogen analyses have noted large deviations from animal to animal. Some of the factors that influence glycogen content are the sex of the animal (7), the age (8), the diet (9), the diurnal changes in liver glycogen (10), and the method for glycogen analysis. We have followed the suggestions offered by Guest and Rawson (9) who obtained 6.9 per cent as the mean value for the liver glycogen content of 50 rats. The average percentage of liver glycogen determined on 22 Decholin and Ketochol-treated rats, who were fed during the last 12 hours, was 5.8 per cent (Table III). The Dechacid No. 14-treated animals were only fed during the last six hours and the liver glycogen averaged only 3.1 per cent. The liver glycogen determination on 6 dogs averaged 5.6 per cent. Thus it can be readily seen that feeding of various oxidized bile preparations over long periods of time did not increase the fat content of the liver or decrease the glycogen content as would be expected if these bile salts were "toxic" to the liver cells.

The histological study of the liver of our animals showed that the cells were normal and that there were no evidences of abnormal fat deposits anywhere in the

TABLE IV  
*Effect of long-continued feeding of 5 grams of oxidized bile salts per day in normal dogs*

Dog	Regime 5 Gms./24 Hours	Weight—Kilos		Total Days	% Retention of Brom. Dye at 20 Min.	% of Total Liver Lipid	% of Liver Glycogen
		Before	After				
1. Male	Decholin (dehydrocholic acid)	11.8	11.8	218	0	3.9	7.2
2. Female	Decholin (dehydrocholic acid)	9.0	10.4	104	0	4.0	5.6
3. Male	Dechacid No. 14 (oxidized ox-bile acid)	8.3	8.8	220	0	4.9	5.5
4. Female	Dechacid No. 14 (oxidized ox-bile acid)	8.9	9.5	132	0	4.5	5.8
5. Female	Ketochol (ketocholanic acid)	7.5	9.2	148	0	4.1	5.6
6. Female	Ketochol (ketocholanic acid)	7.7	9.4	160	0	4.6	4.0

liver. Cantarow (11) has observed changes in the epithelium of the tubules of the cats' kidney after frequent injections of sodium dehydrocholate (Decholin sodium) intravenously. Studies of the kidney sections showed no degenerative changes either in the tubules or glomeruli. Thus, histological studies corroborated our clinical and chemical findings in that they revealed no evidence suggesting that oxidized bile salts act as irritants to the liver and kidney cells, when given orally in the doses used.

### SUMMARY AND CONCLUSIONS

Various oxidized bile salts, dehydrocholic acid (Decholin), ketocholic acids (Ketochol), oxidized conjugated ox-bile salts (Dechacid No. 14), and oxidized conjugated hog-bile salts (Dechacid No. 22) were administered orally to dogs and rats to determine what "toxic" effects they might have on the functional activity of the liver. Toxic effects were examined for

by observing the weight of the animals, by determining bromsulphalein clearance, by analyzing the liver for total fat and glycogen content, and by histological study of sections of the liver and kidney.

The oral administration of 3 and 5 grams of the various oxidized bile preparations daily for 3 to 7 months to dogs and the feeding of 0.3 gm. per kilo daily of these preparations to white rats for at least 1 month resulted in no change in the body weight of the animals, no alteration in the normal bromsulphalein excretion test, and no abnormal changes in the concentrations of total liver fat and glycogen. Histological studies of both the liver and kidney tissues revealed no destructive or degenerative changes in these organs.

Thus, we were unable by the methods used to obtain any evidence indicating that oxidized bile preparations are toxic when given orally in relatively large doses for 3 to 7 months in dogs and for 1 month in rats.

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## Diverticula of the Cardiac End of the Stomach\*

### A Review of the Literature and Report of Three Cases

B<sub>II</sub>

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THE first diverticulum of the stomach was reported by Helmont (1) in 1804. Since that time, more than 140 cases have been mentioned or reported in the literature. Rivers, Stevens and Kirklin (2), in 1935, stated that diverticula of the stomach had been diagnosed roentgenologically in 25 cases at the Mayo Clinic since 1926. Six of the pouches were at the cardia, near the lesser curvature or the posterior wall. Rivers found an incidence of 0.008% of diverticula occurring in the stomach. The autopsy incidence was approximately 0.002%. Cheney and Newell (3), in 1937, reported two instances of gastric diverticula in 11,828 roentgenological examinations done at the Stanford University Hospital in 12 years.

The fact that there has been such a variance of opinion as to the etiology of this condition would lead one to conclude that the etiology is still an unsettled question. Rivers, Stevens and Kirklin (2) applied the term "diverticulum" to a tubular process with a blind end, and Kaufman (4) defined a diverticulum of the stomach as a circumscribed, more or less rounded or

bag-shaped protrusion from the lumen, lined by all three layers of muscle. Gile (5), quoting Terry and Ward in Lewis' "Practice of Surgery," stated that "the true type with intact coats are probably always congenital, while false types are herniae of the mucosa through the muscular coats." Bell and Golden (6) and Emery (7) agree. It is said that at the posterior wall of the cardia, because of the arrangement of the muscle fibers, there is a weak spot. No one has proved this, however. Alvarez (2) has distended fresh stomachs of cats and dogs, under pressure much greater than that obtained physiologically, without producing diverticula. According to Gray (8), viewing the stomach from in front and above, it appears that the right margin of the esophagus is continued downward as the upper two-thirds of the lesser curvature of the stomach. This would raise the question whether these diverticula really are diverticula of the esophagus. Further investigation, however, as a result of roentgenology, esophagoscopy, surgery and autopsy material, does not appear to justify this assumption. It does seem, however, as pointed out by Keith (9) that the wall of the stomach is weak at its junction with the esophagus, so that under certain conditions a

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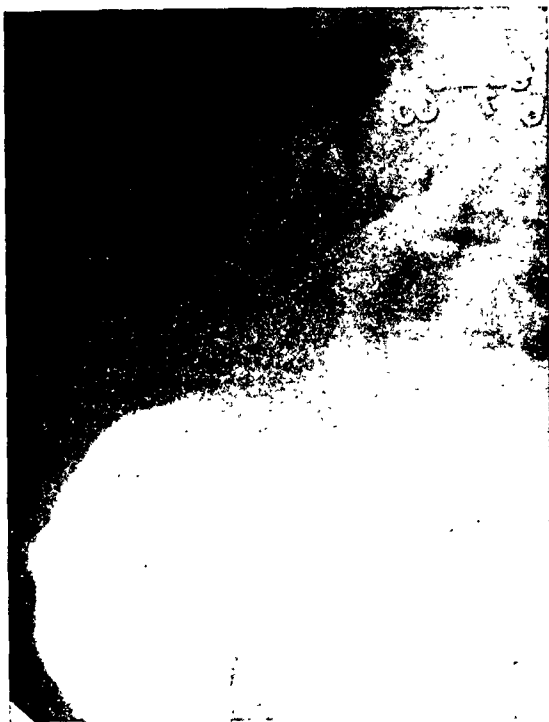


Fig. 1, Case 1. Mrs. E. B. Diverticula observed on posterior wall of stomach in lateral view.

pouch can develop in this area. As stated by Allan (10), it has been shown by X-ray examination that the lesser curvature is a pressure-point on food entering the stomach, and this is offered as a possible explanation why diverticula are more common in this location.

Weiss (11), classified the diverticula into true and false types: Rivers, Stevens and Kirklín (2) suggested: (1) True diverticula are those in which the pouch includes all coats of the gastric wall, without definite evidence that organic disease was the causative factor. These are probably congenital; (2) Acquired true diverticula. In these, all coats of the gastric wall are present, although there may be some thinning. There is evidence that some disease was instrumental in causing the pouching. This type may be grouped as (a) the Pulsion, or (b) the Traction type. (3) False diverticula, or diverticular formation in which there is a break in the gastric wall, resulting from disease.

In reporting the following three cases, two of them seem to fit into class 3, while definite classification of the third is not possible, although congenital origin may be considered. The third patient has remained asymptomatic for a period of two years and has refused to consider surgical intervention.

#### CASE REPORTS

Case 1. Mrs. E. B., a married colored female, age 23, a patient at the Vanderbilt Clinic, was referred to the Gastro-Intestinal Clinic June 3, 1936, complaining of burning in the epigastrium and midsternal region. The patient also complained of daily nausea, vomiting once a week, fifteen to twenty minutes after meals, and sometimes regurgitation of food. When a stomach tube was passed into the esophagus, considerable retention of mucus and food was observed. The patient was placed on daily lavages of

the esophagus for six days, after which a retention of heavy mucus remained, but no retention of food was apparent. X-ray examination of the stomach, March 18, 1935 and May 7, 1935, revealed a diverticulum of the stomach on the postero-mesial side of the cardia. Repeated examination of the esophagus by X-ray showed normal conditions. Gastric analysis on June 5, 1936, showed a normal acid response with some mucus.

A year later the patient returned complaining of difficulty in swallowing, followed by vomiting one hour after eating. Gastric analysis gave no additional information. Roentgenologic examination showed a normal esophagus and the diverticulum with a narrow neck, located just below the esophageal hiatus. The sac seemed to vary in size from time to time. An esophagoscopic examination showed spasm of the cardia, which relaxed after a few minutes. On withdrawing the tube from the stomach, a small opening was found, about the size of a green pea, which opened into an apparent diverticulum. This was thought to be just within the cardia of the stomach. This finding was verified by gastroscopy. Bleeding was noted at gastroscopy, the blood coming from the opening into the diverticulum. Daily lavages were given at home. When the patient was seen again in August, 1937, pain in the epigastrium and left chest persisted. Postural drainage was tried but there was no improvement in the symptoms. Later she was thought to have an exacerbation of a chronic pelvic inflammatory disease, which seemed to make her symptoms worse. Esophageal lavage on October 25, 1937, after a light meal, while a ward patient at the Presbyterian Hospital, showed about 250 cc. of thick mucus with a small amount of food. On lavage of the stomach 200 cc. of residue, which contained little mucus, was removed.

The patient was operated on by Dr. Allan O. Whipple, October 28, 1937. The diverticulum was found on the posterior wall of the stomach near the esophagus. It was about 4 cm. long and had the shape and size of the distal two phalanges of the little finger. Fluoroscopic examination on November 21, 1937, showed no evidence of cardiospasm or obstruction at the lower end of the esophagus. The latter had a normal contour.

Gastroscopy on March 3, 1938, revealed a transverse cleft along the lesser curvature and posterior wall of the cardia, which was taken to be the operative scar. When last seen on September 27, 1939, the patient was feeling fine.

Sections of the diverticulum showed that it was lined by gastric mucosa, which contained many parietal cells. Beneath the glands, the muscularis mucosa was prominent, but the muscularis of the stomach was absent. A few lymphocytes and plasma cells were present in the tissue wall, and there seemed to be a slight increase in the number of these chronic inflammatory cells in a few areas in the deeper portions of the mucosa. The pathologists classified this as an acquired diverticulum, but it would seem to fit best into Rivers (2) class three.

Case 2. Mrs. E. C., a colored female, 26 years of age, was first admitted to The Nassau Hospital, Mineola, N. Y., January 23, 1939, complaining of nausea and moderate pain, of about ten days duration, extending in the midline, from the umbilicus to the xiphoid. The patient stated that she had passed about three ounces of red blood, by bowel, one month previous to admission. The stools had been tarry for the past five days. While carrying her fourth child, she complained of frequent attacks of "heart burn" and indigestion. Since that time, she has had frequent attacks of nausea, flatulence and acid eructations. Baking soda seemed to give her relief. Four years prior to her last pregnancy, her Wasserman was found to be positive. She was treated for this for two years, until the Wasserman became negative.

Roentgenologic examination on February 8, 1939, showed a large diverticulum just below the cardiac orifice. When



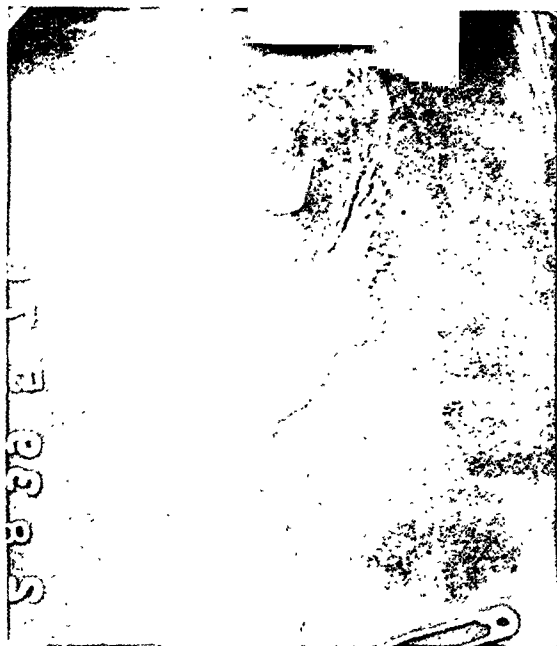


Fig. 2, Case 2. Mrs. E. C. X-ray taken in the antero-posterior view, showing sac located on the posterior wall near the lesser curvature of the cardia.

completely filled it measured three inches in length and remained filled after six hours. The stomach was otherwise normal in tone, peristalsis and contour.

The patient was anemic, with a hemoglobin of 65%, 3,400,000 R.B.C. She was being treated conservatively for pelvic inflammatory disease, but the mass was slow to disappear. On February 14, 1938, she was allowed out of bed and, while going to the bathroom, she had a sudden attack of lower abdominal pain, accompanied by nausea and vomiting. Within two days the hemoglobin dropped from 65% to 47%, with the abdomen remaining relatively soft. A laparotomy was performed February 17, 1939, by Dr. Wilfred M. Post, at which time a ruptured, right-sided, ectopic pregnancy was found. Old pelvic inflammatory disease was found, involving the left tube. On palpation, a diverticulum was felt which was adjacent to the esophagus and had the feeling of being somewhat indurated. There were many adhesions between the diverticulum and diaphragm, as well as between the stomach and liver. Due to the patient's generally poor condition, nothing was done to the stomach. The patient returned to her home on March 5, 1939, with no symptoms relative to the gastro-intestinal tract. She has remained well.

Case No. 3. A private patient, Mr. L. F. R., a white male, 50 years of age, gave a history of having been in several accidents, which may have little or no bearing as a causative factor in the disease. Two years ago, percussion from the explosion of an oil stove struck him in the epigastrium, breaking the skin and causing a second-degree burn. There is no history of operations. He gave a history of having had "bilious attacks" since he was a child, these coming on following heavy meals. When first seen on June 3, 1937, he appeared to have severe pain in the lower left quadrant, radiating to the upper epigastrium and midsternum. This attack was accompanied by nausea and vomiting. The patient gave no history of dyspnoea on exertion, orthopnea or nocturnal dyspnoea. He believed that, at the time of his excruciating pain, there was some radiation of it over the precordium. There was no radiation into the neck or down the left arm. Examination of the heart revealed it to be normal in size and contour. On

auscultation, some roughening of the first aortic sound was noted, but there was no evidence of murmurs heard over the valvular areas. Blood pressure was 140 systolic and 95 diastolic. Examination of the abdomen when first seen revealed tenderness in the epigastrium and left lower quadrant, with no evidence of muscle guarding or rigidity. During subsequent examinations, tenderness was elicited only occasionally in the epigastrium.

Electrocardiographic studies were essentially normal. X-ray examination of the gastro-intestinal tract on June 11, 1937, revealed a normal esophagus. On the lesser curvature side of the cardia, just below the diaphragm lateral to the esophageal hiatus, there was a diverticulum of the stomach, measuring about  $3\frac{1}{2}$  cm. in its longest diameter. The mouth of the diverticulum was narrow, and the pouch emptied poorly with the mass in the erect position. A fluid level was seen. The pyloric antrum was spastic and the mucosal folds in this region were somewhat hypertrophied. There was no evidence of an ulcer. Examination of the pylorus and duodenum were essentially negative. Both six and twenty-four hour examinations, by film, showed a retention of barium in the diverticulum of the stomach.

Since June, 1937, the patient refusing surgical intervention, has been followed at frequent intervals, during which time he has been placed upon an ambulatory regimen for treatment of pre-pyloric gastritis. At night he has employed postural drainage with questionable effectiveness. When seen in September, 1938, he was complaining of considerable phlegm in the mouth, upon awaking in the morning. At no time has he had difficulty in swallowing. When last seen on November 25, 1939, the patient had no gastro-intestinal complaints.

#### COMMENT

Bell and Golden (6) felt that postural drainage should be tried in cases of diverticulum of the cardia. Jordan and Lahey (12) state that treatment should be



Fig. 3, Case 3. Mr. L. R. X-ray taken in the right anterior oblique showing the sac on the posterior wall near the lesser curvature of the cardia.

surgical, for irritation by stomach contents may well predispose to cancer. They add, however, that surgery in this region is frequently impracticable and often impossible, because of difficulty in mobilizing and dissecting the sac. In the case of patients with no symptoms and little retention of food in the diverticulum, it would seem best to temporize.

### CONCLUSION

Three cases of diverticulum of the cardiac end of the stomach are reported. Removal of the sac, in one case, relieved all symptoms. In the second case the patient, untreated, has remained symptom-free for a year, and in the third case the patient has remained symptom-free while using postural drainage.

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## Digestive Tract Infection by the Virus of Lymphogranuloma Inguinale

By

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**C**LINICAL medicine daily opens up new fields for investigation, especially in relation to those problems which up to the present have not been satisfactorily solved and whose ignorance, as regards their true nature, we try to cover up by pompously cataloguing under such terms as "anespecific," "aseptic," etc. Such has been the case with many lymphogranulomatous manifestations of the digestive tract, which have only been defined by associating certain social facts to disease.

Among these facts the most outstanding one and which we started to point out in 1933 (1) is that referring to abnormal sex practices—coitus analis and buccalis—as a possible source of infection of the alimentary canal, which may thus be contaminated by the oral or the rectal routes.

Not only may abnormal sex relations be the cause of infection of the oral cavity; the saprophitism of the virus of lymphogranuloma inguinale was also demonstrated by us in 1933 (1), a fact that has been latterly confirmed by Nicolau (2) and others, on the basis of epidemiological and clinical evidence. Such cases of carriers of latent or attenuated elements of infection may be a source of direct (kisses) or indirect (cutlery) oral transmission of the disease.

Although this last point must be further looked into before awarding it all its possible epidemiological importance, there exists sufficient clinical basis to consider its value, especially if we remember familiar cases of rectal lymphogranuloma described by Dick (3) in a mother and daughter of Sonck (4) who relates the history of 5 girls, ranging from 4 to 9 years of age, who apparently contracted the infection from their diseased mothers and of which 4 had rectal stricture and one an incipient proctitis. It is also of interest, in relation to the point we are debating, to

mention that Brown and Scheifley (5) describe chronic regional enteritis, nowadays considered by many as of possible lymphogranulomatous nature, in 3 siblings all over 20 years of age and that Crohn (6) also details the history of two sisters suffering from regional enteritis.

*Oral penetration of the virus.* Infection of the upper structures of the digestive tract by the virus of lymphogranuloma inguinale have been pointed out by several authors, all of them in relation with abnormal sex practices. Early manifestations of the disease, such as micro-chancres of the lips, tongue, etc., have been described by Buschke and Curth (7), Curth (8), Bloom (9), Coutts (10), Coutts and Saez (11), Nicolau (2), David and Loring (12), Midana (13), Ramos Silva (14), etc. Pharyngitis and tonsillitis of the same nature have been demonstrated by Yamamoto and Mitsumoto (15), Andó (16), etc. In a case of bilateral cervical adenopathy with ulcerative lesions of the tonsils of the Plaut-Vincent type, with intensely positive Frei, Pierret obtained for us a biopsy from one of the tonsils; staining with Mann's classic method we could evidence the existence of numerous micro- and macro-corpules of the type described by Miyagawa and associates in experimental lymphogranulomatous lesions (17). Chronic lesions of analogous nature of lips and tongue were described by us in different monographs. In 1933 (18) we drew the attention to certain forms of glossitis marginata observed chiefly among prostitutes who habitually performed "suctio penis"; in 1934 (19) in an article with Banderas Bianchi and under the heading of "Lymphogranulomatous glossitis marginata and lichen of the tongue" certain lesions such as an enlarged, thickened and furrowed tongue, deep extensive grooves of the dorsum, well limited zones of dark red colour, with loss of superficial epithelium and presenting a lichenoid aspect or opaque leucoplachic

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patches of greyish color; in 1939 (17) we demonstrated a similar etiology for certain cases of chronic keillitis of the simple glandular type. Studying the lips of 31 prostitutes, with Cantin and Sepulveda (17) and who declared habitually practising "suctio penis," in 3 we found chronic fissures of the lips, glandular keillitis and an abnormal thickening of the tongue. All had a positive skin-Frei.

Associated forms of aphthoid and lichenoid manifestations of the mouth and genitalia have been often described by different authors (Montgomery and Culver, Frank, Milian, Périn and Langlois, etc.); Behcet (20) in 1937, describes a symptomatic triad formed by recurrent attacks of iritis along with aphthoid lesions of the mouth and genitalia and in some of which the eyeground findings are very similar to those described by Kitagawa (21), Espildora and Coutts (22) in cases of lymphogranuloma inguinale. Last year, at the weekly Thursday clinical meetings of Prof. Bisquertt's Clinic (Nov. 30) we referred to the history of two patients of our private practice presenting iritis and aphthoid lesions of the penis and mouth. Both had intensely positive skin-Frei's, but negative eyegrounds.

Judging from the confirmed cases and mentioned coincidences we may think that many, up to the present undetermined or wrongly attributed cases of gingivitis, stomatitis, etc., may be caused by the virus of lymphogranuloma inguinale.

Considering what we have exposed in the preceding paragraphs we feel authorized to declare that there exist in the mouth acute and chronic manifestations of lymphogranulomatous nature evidenced by biologic tests and histo-pathological findings—Coutts (17) in tonsils; Romas Silva (14) in tongue.

The question now arises as to whether the constant swallowing of the virus is capable of infecting the alimentary canal and whether this infection proceeds along the mucus surface by contiguous invasion or along the lymphatics of the sub-mucosa.

According to our modest opinion the first question does not offer any doubts; notwithstanding the fact that different epithelia line the surface of the digestive tube and that the virus must come in contact with different secretions, experimental investigations have demonstrated its marked resistance to most common chemical and physical agents. The possible argument of a contiguous ascending mucous infection from a primitive rectal focus in cases of ileo-recto-colitis, can be opposed by the fact that primitive rectal infections of other nature, do not extend upwards by contiguous mucous invasion.

As regards the lymphatic diffusion of the virus we may say, that knowing its marked predilection for such structures and the intimate relationship of pharyngeal, esophageal and gastric lymphatics, such a route of infection is possible.

Acute inflammatory processes of the esophageal and gastric mucosa of lymphogranulomatous nature must exist, chronic lesions as well; but we have at present no positive clinical evidence to ascertain the fact. In a case of esophageal achalasia we had a positive skin-Frei and formol-gelification reaction; in one out of two cases of linitis plastica of the stomach, in men under 40 years of age, we had a positive skin-Frei. Respecting this gastric syndrome, first described by Brinton, it is worth remarking that the condition of partial or

total sclerosis of the stomach with thickening of the walls and reduction of the lumen, may at the same time be accompanied by a similar condition of the colon, small bowel and rectum.

As regards the point we are considering we believe that the following case is of interest.

Case 1. C. D. C. (Santa Clara Ward No. 23, St. Louis Hospital, 2i-III, 1939). Female, aged 23 years. Prostitute. Soft chancre and syphilis in her life record. Six years ago double inguinal adenopathy. Her present illness begins one year ago with certain difficulties to defecate. On examination ulcerations of the vulva and elephantiasis of the labia majora are found. These lesions are at the least of two years standing. Rectal stricture, which by rectoscopy is proved to lie 5 cms. from the anal orifice. Positive skin-Frei and formol-gelification reaction. Positive eyeground for lymphogranuloma inguinale. Wassermann, Kahn and Ito all intensely positive. Deep fissures and hard edematous infiltration of the lips, slight hardening of the free extremity of the tongue. Normal pharynx. Gastroscopy (Dr. Lerner): atypical ulcers of the posterior pre-antral wall. Radioscopic and radiologic investigation of the digestive tube, negative. Normal gastric juice. Patient never complained of gastric symptoms.

The duodenum may be infected contiguously either from a superior bucco-pharyngeal or an immediate gastric focus; it may also be attacked by the lymphatic route. Jamieson and Dobson (23) demonstrated that the lymphatic plexuses of the stomach communicate with those of the duodenum.

Pathologic evidence of lymphogranulomatous lesions of this structure we have not been able to obtain so far. From a clinical point of view and basing ourselves on the gastroscopic findings registered in Case 1, it might be that certain transient duodenal ulcers, accidentally discovered at radiology, and that cure very promptly under simple treatments, are of this nature. This may also be the case of certain other duodenal or peri-duodenal conditions. Personally we have observed such instances happening in two patients who had formerly suffered from lymphogranuloma inguinale (17).

The case we will summarize in the following paragraphs and belonging to our series, we believe to be of interest as regards the aspect we are debating.

Case 2. E. G., 42 years of age. Bilateral inguinal adenopathy in 1936. He confesses to occasional abnormal sex practices (cunnilingus, etc.). Two years after this lymph node inflammation he consults us owing to diffuse abdominal troubles of certain duration, consisting chiefly in gastric pain and a sensation of gastric plenitude. His general health was impaired; asthenia and loss of appetite, also marked psychic depression. Radiological investigation of the digestive tract made at the time by Opazo, showed a marked general thickening of the mucous folds of the bulbar and second portions of the duodenum (duodenitis). Adequate treatment is prescribed but he does not register a very marked improvement.

A persistent diarrhea sets in sometime after and 8 months after his first visit to the capital he consults Dr. Aracena who discovers an infiltrative proctitis and brings him to our consultation at the end of 1938. Positive skin-Frei and eyeground; Wassermann and Kahn tests are negative. Rectal examination reveals the existence of a proliferative rectitis and a marked narrowing of the rectal lumen beginning 4 cms. over the anal orifice. Radioscopic study of the digestive tract reveals the existence of a marked duodenitis of the bulbar and second portions and a stricture of the colon close to the splenic angle. This

lesion that appeared as an annular stricture was permanent in character as proved by successive observations and radiograms with opaque enema taken after injection and after evacuation of the clister. The radiograms taken after evacuation show diffuse changes of all the mucosa of the descending and sigmoid colons below the stricture and over it a retrograde stasis of the transverse colon and caecum.

Crohn and associates (24) isolated in 1932 from the diffuse conglomerate of the intestinal granulomas a clinical entity which they denominated "regional enteritis" and defined it as a pathologic condition of hyperplastic inflammatory type affecting the last 25 or 30 cms. of the ileum. Harris, Bell and Brunn (25) latterly proved that this syndrome could be accompanied by lesions of the jejunum and Brown, Barges and Weber (26) also by lesions of the colon. Further observations induce Crohn (27) to abandon his strictly regional concept of the syndrome and to accept the frequent existence of a concomitant colo-rectitis.

In 1938, Stafford (28) suggests the possibility that the lesions of regional ileitis may be due to the action of a virus, notwithstanding the fact that in 10 cases

pation and severe nocturnal meteorism. Four months after these symptoms had started diarrhea sets in and persists until his entering the Clinic. Since the initiation of his illness he has lost 40 kgs. in weight. Apyretic; lungs and heart normal. Wassermann and Kahn, negative; blood urea 0.40%; hyperchlorhydria; marked indications of albumin in urine; absence of parasites in faeces; red blood cells 3,500,000, white blood cells 8,300. Radiologic study of digestive tract: stomach and duodenum normal; barium totally eliminated at the end of 24 hours. Rectoscopy: erosive catarrhal ano-rectitis. Enema-radiogram of colon reveals an intense colitis. Patient does not improve and dies 21 days after his entering the hospital.

Necropsy shows the existence of a stricture 10 cms. long of the ileum and at 30 cms. distance from the caecum. Over the stricture the intestine is considerably dilated and in the proximal 70 cms. of the stenosis, atrophy of the mucosa and numerous old and recent ulcerations and erosions are evident. Colon presents ulcers and haemorrhagic zones; similar lesions, but of severer type, in the rectal ampulla. Chronic catarrhal amigdalitis. Microscopic study of the ileum at the level of the stricture shows disappearance of the mucosa, which is substituted by fibroblastic tissue and blood vessels. Marked thickening of sub-mucosa and muscularis; the vessels of the sub-mucosa

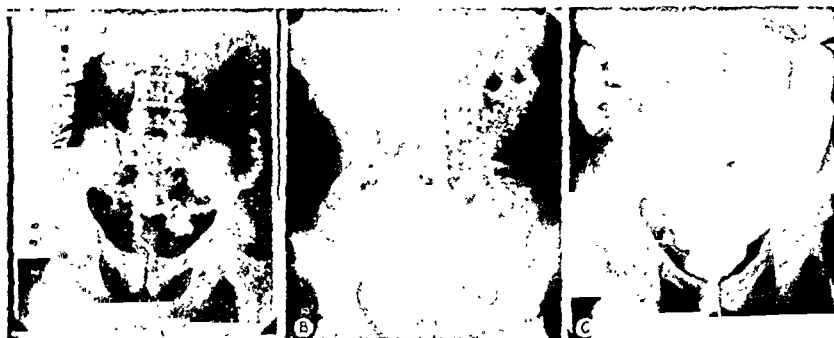


Fig. 1. (a and b) Radiograms taken after evacuation of opaque enema in cases of chronic infiltrative and stenosing recto-colitis. Case corresponding to radiogram b. also presented severe lesions of the ileo-cecal valve and first portion of ileum. (c) Rectal stricture, megasigmoid and stricture at the union of upper and middle thirds of the descending colon. This radiogram corresponds to Case 2.

of this syndrome he could not find one with a positive skin-Frei. Similar findings have also been recorded by other authors (Clark and Dixon, etc.). More recently Lombart and Maneru (29) observed in a patient with a rectal stricture and a positive Frei test, multiple strictures of the ileum.

During the years 1938-39 we were able with Opazo (17) to demonstrate the lymphogranulomatous nature of one case of regional enteritis and of another one of ileo-colo-rectitis. In 1939 with Montenegro (30) we had the opportunity of studying a fragment of ileum from a deceased case of Prof. Alessandri's service, but whose lymphogranulomatous nature was not suspected before death and therefore no adequate tests made. In this case we found in the ileum numerous visible forms of the virus of lymphogranuloma inguinale.

History and evolution of this case are summarized in the following paragraphs:

Case 3. M. H. G. (San Antonio Ward No. 7, Salvador Hospital), 28 years of age. Passed medical history of no importance; several bone traumatism. No venereal diseases. Present illness begins in March, 1939, and is characterized by anorexia, post-prandial gastric plenitude, consti-

are partially obstructed and their tunica considerably thickened. Chronic fibrosis of serosa. Marked general small round cell infiltration. Histo-pathological diagnosis: chronic infiltrative stenosing ileitis.

The cause of death, according to the Pathological Department, was acute peritonitis, owing to perforated regional ileitis.

In 1935, Mocquot, Levaditi and Reinié (31) first mention the possibility of a primitive recto-colitis of lymphogranulomatous nature; in 1936, Goodman (32) demonstrates that the disease picture of ulcerative colitis apparently may be produced by the virus of lymphogranuloma inguinale; in 1938, Stafford (28) obtains a positive Frei test in 3 patients with ulcerative colitis and Paulsen (33) demonstrates the presence of the virus in the stools of such patients and obtains a potent antigen from the faeces. Strictures and ulcerations of ascending, transverse and descending colon of the same nature are mentioned by David and Loring (12), Frei (34), etc.

With Opazo (17), in 3 cases of chronic colo-rectitis we were able to establish radiographically a marked narrowing of the lumen of the large intestine (Fig. 1); biopsies taken from rectal vegetations of these

cases revealed in 2 the existence of visible forms of the virus of lymphogranuloma inguinale. In 4 out of 11 patients with rectal stricture or infiltrative rectitis, studied radiologically in 1938-39, we were able to evidence strictures of different portions of the colon of varying lengths (Fig. 2). Although Ferguson and associates (35) do not consider the possible etiologic role which lymphopatia venerea might play in the production of ulcerative colitis, in 5 patients which they present in their monograph, there is marked narrowing of the lumen of the bowel in every one.

Although most cases of colo-rectal syndromes registered in the medical literature are incompletely studied, as regards the possible existence of lesions in other parts of the digestive tract, based on our cases and observations we are firmly convinced that the virus of lymphogranuloma inguinale can, through the oral cavity, infect any part of the alimentary canal.

The case we will summarily describe in the following paragraphs and which was published in full detail in 1936 (11), and belonging to an epoch when we did not yet think of the possibilities of digestive system

The next we know about him is when we are called in consultation by Saez of Prof. Prado Tagle's Clinic at the Clinical Hospital. Data that follow are taken from the records of this service. In June, 1933,, he suffers from a severe cold and diarrhea (6-8 stools daily). Attending physician diagnoses grippe and prescribes adequate treatment. No improvement as regards diarrhea. Two weeks after the initiation of these symptoms, rheumatoid articular pains and hydrarthrosis of the left knee. Diarrhea continues and stools present a muco-purulent aspect. By the end of August, when he enters the Clinic, he has lost 15 kgms. in weight. Physical examination proves intense emaciation; soft, rapid pulse; tension 14/8; fever. Fibrosis of sub-maxillary and cervical lymph nodes; left hydrarthrosis. Heart and lungs normal, both clinically and radiologically. Radiogram of recto-colon reveals the existence of a stricture at the union of the descending and sigmoid colons. Rectoscopy demonstrates the existence of a partially ulcerative procto-sigmoiditis of the chronic catarrhal type and of a sphincteric acute proctitis. Wassermann and Kahn, negative; erythrocytes 1,800,000, leucocytes 4,100.

General condition of the patient daily becomes worse and his family removes him from the hospital. He dies at home in December of the same year.



Fig. 2. (a) Radiogram obtained after opaque enema; stricture of the rectum, infiltration of the ascending colon-tubular narrowing of lower 2/3, stricture of the upper third of the same portion. (b) Same case after evacuation, confirming aforementioned lesions. (c) Stricture of the rectum accompanied by tubular, rigid, stricture of all the ascending colon; intense infiltration of splenic half of transverse colon.

descending infections is, according to our modest opinion, of great value as a demonstration of the theory that we have sustained in this sub-title of our monograph.

Case 4. X. X. X., 25 years of age. Law student. Gonorrhea in 1926. His present illness begins in August, 1932, with a small penile chancre and subsequent left inguinal adenopathy. He consults one of us and Darkfield, Ito, Wassermann and Kahn tests are found to be negative. Frei intensely positive. Information as regards abnormal sex intercourse with women is positive. He is treated with Fuadin and radiotherapy but with no results. As the lymph nodes break open he feels dissatisfied with our medical care and consults another physician who excises all damaged inguinal lymph nodes. Shortly after this operation left sub-maxillary lymph nodes increase in size and a few days later similar ganglia to the right show signs of inflammation; both processes soon break down, fester and sinuses are formed. In these conditions he decides to place himself once again under our care. Interrogation reveals that during his illness he has occasionally practiced crossed cunnilingus with the woman who lives with him. Wassermann and Kahn tests negative. Submitted to local and general treatments his conditions improve and after two months we lose sight of him again.

Before ending our considerations on this aspect of the problem we will mention that Brulé (36), in 1937, described under the denomination of "cellulite de la nuque" a painful infiltration of the cellular tissue and muscles of the back of the neck, accompanied by the formation of nodosities. Such a condition we have found to exist in 4 out of 20 prostitutes with genito-ano-rectal syndromes of lymphogranulomatous nature. All of them habitually practiced "suctio penis."

**Rectal infection.** The rectum may be attacked by the virus of lymphogranuloma inguinale directly from its interior or indirectly from primitive genital foci.

(a) Direct or rectogenous infection. The rectogenous penetration of the virus is associated with pederasty in men and with anti-conceptual anal coitus in women. The first symptoms of infection are usually not recorded by the patient; occasionally they remember having suffered from a slight anal discharge and tenesmus.

Once infection is produced the virus penetrates the deeper layers through dermo-mucous abrasures of the anus or through the inflamed mucosa. Peri-anal and

peri-rectal lymphatics constitute the most common routes of propagation. This type of infection is usually accompanied by the formation of peri-anal and rectal vegetations; non-papillomatous condylomata may also be found around the anal orifice. The proliferations of mucosa or dermo-mucosa contain large numbers of granulo-corpuseular forms of the virus. We have investigated their presence in 6 non-papillomatous condylomata of the anal margin and found them in every case. Following rectal infection inflammatory symptoms may subside or may gradually increase in severity; especially noticeable is the appearance of frequent muco-purulent stools and intense tenesmus. The formation of peri-anal abscesses and draining sinuses is, in some cases, an early complication; in such cases they precede by months and even years the installation of a stricture. As the disease progresses new abscesses appear around the anus or in the ischio-rectal fossae. The character of these abscesses is intensely inflammatory, in contrast to that of the early period ones, whose nature is tuberculoid. These latter period abscesses we attribute to secondary infections produced principally by colon bacilli who invade the peri-rectal cellulose-adipose tissues through supra-strictural ulcerations.

Dimitriu and Stoia (37), based on the study of a large material have the impression, that if in general terms the lymphatic vessels constitute the means of propagation of the disease, the virus can directly attack the tissues of the rectal wall. This fact is correct as we have been able up to the present to demonstrate in 12 (85.7%) out of 14 biopsy fragments of diseased rectal wall, especially vegetations, the presence of granulo-corpuseles. According to them, in numerous laparotomies performed in cases of infiltrative rectitis, the larger number of peri-rectal lymph nodes are not diseased and they have never observed a sinus having a lymph node as its starting point. On the basis of these findings they diminish the importance awarded to lymphatic stasis. On the contrary we believe that their findings increase the importance of stasis. Deep lymph nodes seldom break down, such as is the case with iliac and other lymph nodes, but their inflammation favors stasis and the bursting of lymphatic vessels, owing to the formation of lymphothrombi in the lumen, as proved by Barthels and Biberstein (38), Coutts and Martini (39), etc., and the subsequent infection of the cellular tissue with the formation first of tissular micro abscesses and latterly of larger collections owing to confluent fusion of the smaller processes. Sinuses start from such active nests and not from the lymph nodes as correctly observed by Dimitriu and Stoia (37). The type of stricture in the rectogenous infection is usually a low one, from 2-6 cms. over the anus. Very low situated forms are more common. Rectal inspection either with the anoscope, or with the recto or urethro-scope, allows us to establish the existence below, at the level and over the stricture. Below the stricture the mucous membrane is red, has lost its elasticity and is strewn with vegetations; sometimes ulcers are found. The anus presents ulcerations of a fissural type and not uncommonly clumps of non-papillomatous condylomata are observed. On the surface of the stricture hardly ever have we found ulcerations; small bleeding traumatic fissures can be observed at its level when drawing away the tube. The mucous membrane appears as intimately fused to the underlying fibrous

tissue. Above the stricture an extension of the inflammatory lesions of the mucosa, an infiltration of deeper layers and ulcerations can be observed. These ulcerations are probably non-lymphogranulomatous in nature; they are probably due to necrobiosis following fecal pressure and later colon bacilli infection.

We have not seen this type of infection extending to the sigmoid or descending colon. It is practically a localized ano-rectal process, that often invades peri-rectal cellulose-adipose tissues with subsequent formation of abscesses and sinuses. Peri-anal excrescences are very commonly observed in both sexes.

(b) Indirect or lymphogenous infection. Lymphogenous penetration of the virus presents certain important aspects, especially in relation to sex and differences in lymph drainage. In man, infection of the posterior urethra and prostatic utricle owing to the lymphatic collectors of these regions that drain into the posterior lymphatic pedicles of the prostate gland, may reach, according to Nesselrod (40), Parker (41), etc., the rectal absorbent pedicles and originate peri-rectal infiltrative processes. Owing to the lymphatics involved the most affected regions are the middle and upper thirds of the rectum.

In women, rectal strictures of this origin may be low, intermediate or highly situated ones. In the first form they are associated with chronic ulcers of the vulva or esthiomene; in the second and third types, with lymphogranulomatous processes of parametria—Franchi (42)—Fallopian tubes—D'Aunoy and Schenken (43)—or ovaries—Coutts et al (44).

Chronic lymphogranulomatous ulcers of the ostium or external lower portion of the vagina may determine, through infection along the minute skin lymphatics surrounding the ano-vulvar region, an infection of the anus and lower rectum. Combined vulvo-anal bidigital palpation in such cases seldom fails to demonstrate a varying degree of fusion of the affected vulvar region and rectum, immediately over the anus.

Inoculation of the virus upon the posterior surface of the upper vaginal mucosa or posterior lip of the cervix is more prone to invade the deep pelvis lymph nodes that surround the middle and upper thirds of the rectum. Many lymph vessels lead from this region posteriorly through the rectal fascia and utero-sacral lymph channels to the rectal wall and drain into the peri-rectal lymph nodes to a height of from 8-10 cms. (Nesselrod). The same can be said in relation to tube and ovarian infections.

Owing to the passage of the virus into the adipose and cellular tissues surrounding the rectum, deeply seated lymphogranulomatous abscesses may be formed. Some of these abscesses may open around the anus, in the ischio-rectal fossae or gluteal regions. They commonly precede by years the installation of a rectal stricture.

Stenosis of the rectum when associated with pelvic lymphatic infection presents, as shown by us in 1934 (45), certain characteristic aspects. The narrowing of the rectal lumen has an exogenous origin, the infiltrative process is first peri-rectal and latterly gradually invades muscularis, sub-mucosa and mucosa.

Owing to the afore-mentioned mechanism of formation, for years the patient records the passage of flattened stools and increasing signs of constipation. The inflammatory symptoms are, in our opinion, due

to the supra-strictural stasis of advanced stages of the condition. Rectoscopy, excluding cases of low genital penetration of the virus in women and to which we have made reference, reveals two outstanding facts: first, that the stricture is long (4-8 cms.) and tubular, as proved by radiograms (Fig. 3); secondly, that in most cases the mucus surface below the stricture shows no or very few inflammatory changes, in contrast to those registered over it. This explains the absence of peri-anal excrescences.

Inspection of the stricture proper, which in advanced cases is very easily made with the urethroscope, shows disappearance of the mucosa and intimate fusion of rectal layers. In highly situated strictures of this type it is not uncommon to observe an extension of the process to the sigmoid colon (Fig. 3).

Although the peritoneum does not form part of the alimentary canal it nevertheless lines the abdominal cavity and forms a more or less complete covering for many parts of the digestive system. Many inflammatory conditions of this serous membrane are in relation to lymphogranulomatous infection of strictures con-

in Prof. Alessandri's service a very interesting case whose history and clinical evolution we summarize.

Case 5. S. C. P. (Maximo Hertel Ward No. 24, Salvador Hospital, 24-v. 1939), workman, aged 38 years. His present illness begins suddenly 6 days ago, with shivering, cough, mucoid sputum and intense pain under the right costal margin. At the same time meteorism, constipation and impossibility to pass gasses. A forementioned symptoms do not subside under inadequate treatments and he is brought to the Hospital. He had noticed a marked inflammation of right inguinal lymph nodes for some days before the installment of his present troubles.

The Emergency Service of the Hospital finds symptoms of intestinal obstruction and prescribes atropin, hypophisin and intravenous injection of hypertonic sodium chloride solution. Under this treatment his bowels open freely and his condition rapidly improves. Clinical examination and laboratory investigations do not reveal any other pathologic condition. Frei positive; biopsy of an excised lymph node proves its lymphogranulomatous nature. He is treated with sulphapiridyne.

The conclusions we arrive at, based on the study of 72 cases of digestive system lymphogranulomatous

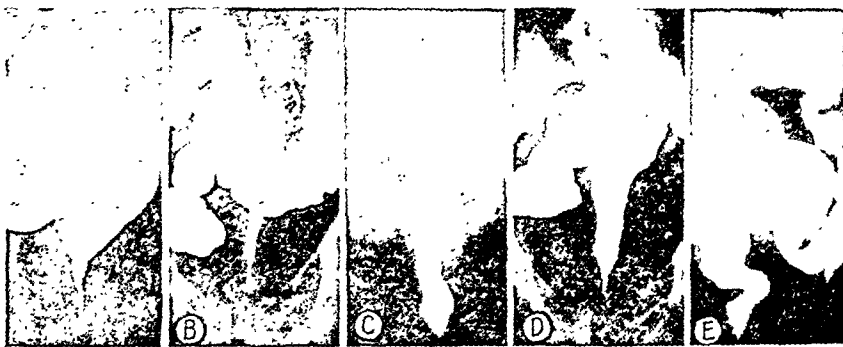


Fig. 3. Radiograms of rectal lesions due to lower route penetration of the virus taken after opaque enema. (a) Rectogenous or direct penetration, low stricture and marked distention of the sigmoid. (b) Rectogenous penetration; process extending to the peri-rectum. (c, d and e) Lymphogenous indirect infection; long, tubular type of stricture.

tained in the abdominal and pelvic cavities or in contact with it. Acute peritonitis produced by the virus of the disease is demonstrated by Kondo (46); peritonism of the lower abdomen, in relation to deep iliac lymph node inflammation as well as of the right upper abdominal quadrant, as proved by Fitz-Hugh (47) and others in different infections of pelvic structures, has been recorded by us in several cases (48); adhesions between intestines and female genital organs containing visible forms of the virus have also been described by us (49); Tengwall (50) publishes a case of lymphogranuloma inguinale with peritonitis and strangulation ileus; in our country Martini Herrera (51), observes another case of upper right abdominal quadrant peritonism in a man with inguino-iliac lymphogranulomatosis and Martha Montenegro studies

syndromes studied during the years 1937-39, are of a medical and a surgical type.

As regards the first aspect, we must draw attention to the possible descending infection of the alimentary canal and the existence of inflammatory conditions that require appropriate treatment and diagnosis.

Respecting the second aspect, we emphasize the necessity of classifying rectal lymphogranulomatous conditions, and performing a careful radiological investigation of the ileum and colon before performing radical operations. We also recommend prudence in the presence of such conditions and not precipitate surgical procedures under any conditions before treating the patients with sulphapiridyne or similar compounds.

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## Results of the Questionnaire on Fatalities in Gastroscopy

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IN October, 1939, I published a questionnaire in this periodical with the hope of finding out if there have been any fatalities due to use of the flexible gastro-scope. In this questionnaire I asked gastroscopists the following questions: (1) Have you ever observed a death, following gastroscopic examination, which you attributed to traumatism caused by the instrument? Were the recognized contra-indications excluded? (2) How many gastroscopies have you carried out? This questionnaire was answered by sixty gastroscopists from the United States, England and Australia. Some writers did not mention the number of gastroscopies carried out, but simply stated that they had not seen any bad consequences. Their reports have been omitted in the following discussion.

In all, 22,351 gastroscopies were reported. The minimum number reported by any one gastroscopist was 15, and the maximum was 3,405. Fifty-one of the sixty observers reported that they had had no serious complications. There was one fatality which will now be reported in detail.

Submitted April 8, 1940.

A woman, 56 years of age, had anorexia for three months, constipation for five years, marked flatulence and heavy feeling in the epigastrium for five years coming on one-half hour after meals. There was a loss of 16 pounds in two years. For six months she had had a dry, hacking cough. A few weeks before the entry into the hospital the presence of a left hydrothorax was recognized. The X-ray examination, carried out after admission, showed a marked "left hydrothorax with fibrous pleurisy." A possible left hilar bronchiogenic carcinoma was suspected. A barium meal demonstrated persistent narrowing of the fundus of the stomach. There was no conclusive evidence of a filling defect. The following procedures were performed on this patient for diagnostic purposes.

4/26/39	Bronchoscopy
5/ 1/39	Thoracoscopy
5/ 3/39	Artificial pneumothorax
5/ 5/39	Sternal puncture
5/ 9/39	Gastroscopy

On 5/6/39, ten days after the bronchoscopic examination and three days before the gastroscopic examination, the temperature rose to 39°, gradually subsiding before gastroscopy. The gastroscopic examination was easily performed by experienced and well trained observers.



Atrophic gastritis of patchy distribution was seen, but no evidence of tumor. No difficulty was encountered at the introduction of the flexible gastroscope; and no blood was seen to cover the instrument after the withdrawal. Four hours after the gastroscopic examination the patient's temperature rose to 39.5°, and she complained of marked pain in the neck and difficulty in swallowing. By the next morning she developed a marked swelling about the left neck with subcutaneous emphysema. A perforation of the upper esophagus was suspected. Immediate X-ray examination revealed the mediastinum shifted to the right due to air in the left chest. It was questioned whether the source of this air was from the esophagus, or whether it was due to a rupture of the visceral pleura.

In the following days there was a marked improvement of the condition. The patient was treated with an ice-collar and did not receive any food by mouth. However, on 5/14/39, the temperature suddenly rose again; and on 5/17/39, a diagnosis was made of "an abscess in the left hypopharyngeal region, pushing forward and deflecting the laryngeal structures." On 5/18/39, the ninth day following gastroscopy, dyspnea and cyanosis developed very suddenly. Tracheotomy was attempted, during which procedure the patient expired. As the trachea was approached large amounts of pus welled up into the wound. It was thought by the surgeon that this paratracheal abscess had produced tracheal compression. Acute circulatory collapse was deemed to be the immediate cause of death. At autopsy a diffuse carcinomatosis of the left lung and pleura was found. Evidence of heart disease and acute cardiac collapse was found; and a small perforation of the esophagus, posteriorly at the level of the seventh cervical vertebra, with a large abscess present in the posterior mediastinum at this level was also found.

This is the first case of hypopharyngeal lesion encountered after closed tube gastroscopy. Even in the dangerous times of the rigid gastroscope, such a lesion was never noted. This was an interesting fact because a lesion of the hypopharynx with subsequent subcutaneous emphysema, formation of abscess, and mediastinitis, is the most common lesion following open tube procedures such as esophagoscopy and bronchoscopy. In spite of the fact that the gastroscopic examination was unusually easy, and no difficulty was experienced in overcoming the sphincter muscle of the pharynx, we must attribute this death to flexible tube gastroscopy. The course, however, was a very remarkable one. In an extremely weak patient suffering from lung carcinoma, many major diagnostic procedures were carried out within two weeks. Gastroscopy was the last of these procedures, and it should be noted that the temperature went up to 39° three days before the gastroscopic examination. An explanation for this rise of temperature has not been given in the report, but I am not convinced that it had nothing to do with the bronchoscopy carried out seven days before. One may speculate that at bronchoscopy a small lesion of the hypopharynx had been produced and that the slight trauma of gastroscopy had been sufficient to cause a complete perforation at the injured place. Since it cannot be proved, this experience should teach us not to go ahead with flexible tube gastroscopy if an open tube procedure has been carried out previously, the after effects of which have not been definitely overcome.

9 other complications which were *not fatal* were reported among the 22,351 gastroscopies, 8 of them being perforations of the gastric wall, and one a perforation of the jejunum. Case reports of 7 of these perforations have been published (1, 4, 5). Five perfo-

rations of the stomach could be attributed to the friction of the rubber sponge tip, which has now been discarded. The 3 other cases, however, teach us that such perforation is possible with the finger tip. Three of the patients were treated conservatively; the others were operated upon. The gastric lesions were always found in the upper portions of the posterior wall. The recovery in all cases was an uneventful one.

Bergh, Bowers and Wangenstein (1) carried out dog experiments in order to determine the danger of perforations of various portions of the gastro-intestinal tract. Perforations of the dog's stomach, if empty, caused a mortality of only 6.9 per cent. When the stomach contained food the mortality was 86.7 per cent. The mortality following perforation of the duodenum was 81.2 per cent; that of the jejunum, 44.4 per cent; and that of the terminal ileum, 100 per cent. It is obvious that the condition of the stomach at gastroscopy is very favorable for spontaneous healing of a perforation because the stomach is entirely emptied immediately before the procedure. Therefore, it seems justifiable to treat patients with such a condition conservatively, although immediate laparotomy probably is the better procedure.

The diagnosis of such a lesion can be made, and should be made immediately. When the examiner tries to inflate air into the stomach he will be unable to get a picture of the gastric wall; the air will escape, and the gastric wall will collapse continuously. Such an observation should lead to immediate fluoroscopy which will reveal air below the diaphragm. In one case, not included in the group mentioned above, this characteristic syndrome was not observed. The gastroscopic examination was performed and revealed atrophic gastritis; but the day after the gastroscopy air was found in the peritoneal cavity. An explanation of this cannot now be given.

In another patient, sent for gastroscopic examination with a provisional diagnosis of cardiospasm, the gastroscopist decided to consider this as a contra-indication and would neither anesthetize the throat, nor introduce a tube or the gastroscope. Forty-eight hours later the patient developed a sudden, severe pain in his epigastrium, abdominal rigidity, and leucocytosis; and a scout plate of his abdomen revealed air underneath both diaphragms. He expired with a typical picture of peritonitis, having refused surgery. A post mortem was not permitted. The gastroscopist who referred this case adds the following comment: "Had any attempt been made to gastroscope this patient, without doubt the instrument would have been blamed for producing this picture." This agrees entirely with the report of a similar case by Moutier (3).

One disagreeable event which occurred five minutes after the gastroscopic examination evidently could not be attributed to the procedure. The gastroscopic examination in a quiet and very reasonable patient had been extremely easy and the patient left the table without any inconvenience. Five minutes later he started to cough convulsively, and pneumothorax developed. No infection occurred and no rise of temperature was observed. Thus it was obvious that there was no perforation of the esophagus, but only a spontaneous pneumothorax. Perforations of the lower esophagus were, unfortunately, very well known in the times of the rigid gastroscope. The symptoms of this

lesion are so characteristic that they can not be mistaken. The patient collapses during the examination, and mediastinal infection leads inevitably to death in a very short time.

It should be mentioned that one of the gastroscopists told in his letter that he had had no bad effects after gastroscopy, but had seen two perforations of the stomach during X-ray examination. Perforations of gastric ulcer during X-ray examination are well known, and the situation at such an event is much more serious than if it occurs at gastroscopy because at X-ray examination the stomach is filled with barium. However, this accident happens so rarely that it scarcely deserves consideration.

Accidents following the anesthesia do not belong properly to the question of the danger of gastroscopy. However, a few notes on the toxicity of pontocaine used generally for the anesthesia at gastroscopy are in order. It seems that pontocaine is definitely dangerous when used in the presence of open wounds or on the mucosa of the trachea and of the bronchii. Its toxicity when used in reasonable amounts on the squamous epithelium of the pharynx and esophagus seems to be insignificant. However, three deaths have been observed following the use of pontocaine in gastroscopy. 2 of them have been reported by Hancock (2). In both of them the patient was extremely cachectic, suffering from carcinomatosis. A third death was reported to me. This patient also had multiple metastases of carcinoma. He developed convulsions and died in spite of intravenous barbiturate injections.

I, myself, once ran into a dangerous situation in an emaciated patient with stricture of the esophagus (not at gastroscopy). After application of 3 cc. of pontocaine he developed convulsions, especially of the scalp; the pupils became wide; the pulse could no longer be felt, and the respiration came to a stand-still. The intravenous injection of pentothol sodium was followed by the immediate disappearance of the symptoms.

In my opinion the conclusions to be drawn are: As used in gastroscopy, pontocaine does not have a great toxicity, but the amount previously recommended

should be reduced, and not more than two injections of 2½ cc. of the 2 per cent solution should be used. Adrenalin should be added to the solution. No pontocaine should be used in the case of an emaciated patient. If toxic symptoms should develop, intravenous injection of pentothol sodium should be made immediately.

I did not expect to find such a favorable result from the questionnaire. It was to be expected that awkward instrumentation or lack of adequate training would lead to many complications. It seems now that flexible tube gastroscopy is one of our safest diagnostic procedures. This experience, however, should not permit us to become careless. We always will have to realize that every endoscopic procedure will involve danger, and that only continuous observation of the contraindications and of the special condition of the individual patient will prevent us from inflicting injury.

### SUMMARY

60 gastroscopists reported their experience during 22,351 gastroscopies. In this series there was one death which probably has to be attributed to the use of the gastroscope. Thus the fatality of gastroscopy is 0.004 per cent, or practically nil.

Eight perforations of the stomach, and one perforation of the jejunum in a resected stomach, have been observed. All patients recovered either after conservative treatment or after surgical interference.

Other complications have been mentioned, and the toxicity of pontocaine for the anesthesia in gastroscopy has been discussed.

I want to thank all colleagues whose extensive, detailed reports made this survey possible.

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## Digestion and Absorption in a Man with all but Three Feet of the Small Intestine Removed Surgically

By

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and

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THE present paper summarizes the findings of three periods of metabolic study carried out on Subject H who has suffered from regional ileitis for a number of years. As a result of five resections only three feet of small intestine remain.

The results of the first study, carried out in 1935,

have been reported (1). The clinical history of the patient was discussed there and will not be repeated. The same general procedures and methods of analysis as reported in the first paper have been used throughout this study.

The patient was admitted to the hospital (4-5-35) in a state of tetany associated with a blood calcium of 6.5 mgs. per 100 cc. of serum. Following relief of the

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tetany by intravenous calcium, Vitamin D (viosterol) and calcium gluconate were given by mouth and the patient gradually improved.

In each of the three periods of study balances were determined for the following substances: carbohydrate, nitrogen ( $\times 6.25$  for protein), fat, and calcium and phosphorus. The caloric balance was calculated from these data. Thirty minims of viosterol were administered daily throughout the periods of study.

**First Period:** The first period of metabolic study extended from June 18 to June 24, 1935, inclusive. At this time the patient had a blood calcium of 8.0 mgs. per 100 cc. of serum and was definitely improved. The results of this period of study as well as the following two are given in Table I. It will be seen that the patient utilized 99+ per cent of the carbohydrate ingested, 75 per cent of the protein, but only 55 per cent of the fat. Fecal fat consisted of about 80 per cent fatty acids, indicating a fair degree of fat digestion. Considerable of this fat digestion may have taken place after the food reached the large intestine, in which case it would not have been absorbed.

During this seven day period 18.47 gms. of calcium were taken in and 14.82 gms. excreted representing a positive balance of 3.65 gms. Of 15.33 gms. of phosphorus ingested 13.08 gms. were excreted; a positive balance of 2.25 gms. for the period. The large amount of fatty acids in the feces undoubtedly caused excessive loss of calcium through calcium soap formation. The urinary calcium averaged only 41 mgs. per day. Additional factors which kept the calcium requirement so high were the greatly reduced absorbing area of the intestine and the increased rate of movement of food through the intestine; the latter occasioned by a moderate and constant diarrhea. At any rate the very high calcium intake was not far above the requirement to maintain a positive balance.

The patient was discharged from the hospital June 25, 1935, and instructed to continue a high calcium and Vitamin D intake. On August 1, 1935, his blood calcium was 9.2 mgs. per 100 cc. of serum and it was the same on October 12, 1935. At this time he was able to do light work.

The patient was readmitted to the hospital in February of 1938 in tetany; his condition on the whole was worse than at the time of his previous admission. After some improvement following high calcium and Vitamin D (viosterol) ingestion a second metabolic

study was carried out. At this time the patient was allowed, as in the first study, to select his food a la carte which again resulted in a high fat diet. **Second Period:** March 2 to March 10, 1938, inclusive.

In this period carbohydrate and protein were utilized to the same extent as in period 1. The fat intake was very high, 200 gms. per day, and only 38% was utilized. The remainder again appeared in the feces in large part as digested fat. This large loss of fat in the feces is reflected in the calcium metabolism. With an intake of over 3 gms. of calcium per day (as food and calcium gluconate) plus Vitamin D as viosterol the balance was  $-2.35$  gms. for the period. Under somewhat similar dietary conditions during period 1 (15% lower fat intake and 30% lower calcium intake) the subject maintained a positive calcium balance of 3.65 gms. for the period. It would appear from this that the increased fat ingestion and its decreased utilization during period 2 were sufficient, even in the presence of large amounts of calcium and Vitamin D, to decrease calcium absorption to a dangerously low value. Urinary calcium averaged only 41 mgs. per day during this period. The phosphorus balance was slightly negative ( $-1.24$  gms. for the period) and may be accounted for on the basis of poor calcium absorption. **Third Period:** April 17 to April 24, 1938, inclusive. High carbohydrate diet.

In period 3 while ingesting 500 gms. of carbohydrate daily, the carbohydrate was again practically all utilized while protein metabolism was slightly less efficient than in the two preceding studies. During this period the subject was allowed only about one-half as much fat as during the previous studies (97 gms. per day). It is apparent from Table I that with this lowered fat intake the percentage absorption was decreased tremendously; only 5.3% utilization. However, the absolute amount excreted was only a little over half the quantity excreted during the preceding period. This lowered excretion is again reflected in the calcium metabolism in a manner as might be expected, for the negative calcium balance of 2.36 gms. during period 2 (9 days) was reduced to a negative balance of 1.0 gm. during period 3 (7 days). The daily calcium intake was virtually the same during the two periods as was the urinary calcium excretion.

Phosphorus was brought into slight positive balance which probably follows from better calcium absorption.

TABLE I

*Summary of food intake and excretion (in grams) by subject H during three periods of metabolic study*

Food	1 7 Day Period 6-18 to 6-24 '35 Inc. High Fat Diet			2 9 Day Period 3-2 to 3-10 '38 Inc. High Fat Diet			3 7 Day Period 4-17 to 4-23 '38 Inc. High Carbohydrate Diet		
	Int.	Exc.	Per Cent Used	Int.	Exc.	Per Cent Used	Int.	Exc.	Per Cent Used
Carb.	1851	13.6	99+	2922	14.26	99+	3565	20	99+
Prot.	932	226	76	1225	308	75	1139	354	69
Fat	1181	531	55	1795	1105	38	679	643	5.3
Ca	18.47	14.82	+3.65 gm.*	26.06	28.42	-2.36 gm.	20.63	21.63	-1.0 gm.
P	15.33	13.08	+2.25 gm.*	20.89	22.13	-1.24 gm.	17.64	17.43	+0.21 gm.
Cals.	21761	5737	74	32752	11234	66	24923	7282	71

\*Calcium and phosphorus are given as + and - grams in order to show the state of metabolic balance.

TABLE II

Average daily intake and utilization of foods (in grams) and calories by subject H during the three periods of metabolic study

	Period I 6-18 to 6-24, 1935, Inclusive		Period II 3-2 to 3-10, 1938, Inclusive		Period III 4-17 to 4-23, 1938, Inclusive	
	Intake	Used	Intake	Used	Intake	Used
Carbohydrate	264	262	325	323	509	506
Protein	133	101	136	102	163	112
Fat	169	93	200	77	97	5
Calories*	3110	2289	3644	2393	3561	2517
Ca	2.64	+0.52*	2.90	-0.26	2.95	-0.14
P	2.19	+0.32*	2.32	-0.14	2.52	+0.03

\* + and — figures show average daily Ca and P metabolic balances.

Table II gives the calculated average daily intake and the utilization of the various substances studied during the three metabolic periods. The data are more easily appraised in this form.

A point of some interest is the caloric loss during each of the three periods which obviously resulted from poor utilization of protein and fat. In period 2 the absolute fat loss was greatest and accounts in large part for the utilization of only 2395 calories out of 3644 ingested. In period 3 only 5.3 per cent of the fat was utilized but because the total intake was much less the net caloric loss was not as great in period 2.

The results of the above experiments seem to indicate the advisability of a relatively high carbohydrate-low fat diet, together with high calcium and Vitamin D, in such cases.

#### SUMMARY

Metabolic studies were conducted on a case of regional ileitis possessing only three feet of small intestine. Balance experiments on carbohydrate, protein, fat, calcium and phosphorus were carried out. Caloric

utilization was calculated from the data obtained.

Carbohydrates were utilized normally in all three periods of study. Proteins were not as well absorbed; 76%, 75% and 69% for the three periods. Of more interest is the fat metabolism due to its direct effect on calcium absorption. The data indicate that more calcium was lost when larger amounts of fats (largely as fatty acids) were excreted in the feces. Phosphorus excretion tended to parallel the excretion of calcium.

Tetany was obviated only by a very high calcium and Vitamin D (viosterol) diet and was controlled more easily with a high carbohydrate-low fat intake (Period 3).

The writers are indebted to Dr. Paul I. Carter, Manager; Dr. R. W. Brace, Chief Medical Officer, and Misses Margaret Beach and Ella Larsh, Dieticians, of the U. S. Veterans Hospital, Portland, Oregon, for their co-operation in making this study possible.

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## Fecal Impaction Due to a Hygroscopic Gum Laxative

By

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MR. A. C. T., aged sixty-eight years, was first seen on October 12, 1937, when he was suffering with what was diagnosed as an acute exacerbation of chronic appendicitis. He had also a mild diabetes mellitus, benign hypertrophy of the prostate, and generalized arteriosclerosis. The acute phase of appendicitis subsided in several weeks, and the patient returned home. A fluoroscopic examination of the colon was made three weeks after the patient was discharged from the hospital. Tenderness still was present in the region of a nonfilling appendix. Neither spasm in the ileocecal region nor other additional disease was noted. Examination of the stools was negative at this time.

Six months later the patient again was admitted to the hospital. He had been symptom-free since his

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previous admittance. Three days before the patient suffered from loss of appetite and general malaise. The next day abdominal pain appeared in the right lower quadrant. Obstipation and marked abdominal distention followed shortly and lasted for four days. Moderate abdominal distention and marked tenderness in the right lower quadrant were present. Peristaltic sounds were decreased. Rectal examination was negative. Perhaps because of the abdominal distention, no mass was felt in the abdomen. The knees were flexed on the abdomen for relief of pain. The temperature was 102°, pulse 110, and respiration 24. The urine showed albumin 2+, sugar 4+, acetone 3+ and diacetic acid 1+. The leukocyte count was 14,500. All other physical and laboratory data were essentially normal. It was believed at this time that the patient was suffering from a recurrent attack of acute appendicitis

with possible abscess formation. The complication of foreign body obstruction was not suspected. It was thought advisable to defer operation and treat the patient conservatively.

Three days after admission the patient was better; the temperature was almost normal; only a slight leukocytosis persisted, and the abdominal pain had disappeared. Flatus had been passed, and hyperperistalsis was present. Repeated small soap suds enemas had been given with only the passage of flatus.

Three days later a cylindrical smooth mass was palpated in the right side of the abdomen. After the patient had been given a large soap suds enema, six hard black masses were removed manually from the rectum. They varied in size from a lime to a lemon. These were identified as dehydrated Saraka.

From March 1, 1939, to April 1, 1939, the patient had taken two or three drums of Saraka each night at bedtime with only enough water to get the material down. He had not taken any for two weeks before his admission to the hospital.

The patient improved rapidly and has remained well

on a low-residue diabetic diet. An interval appendectomy was suggested but has been refused.

On the first admittance to the hospital the patient appeared to be suffering from acute appendicitis. The question must be raised whether on the second admittance the patient again was suffering from a recurrence of his earlier disorder as well as the fecal impaction. In retrospect it is believed that ileocecal spasm in the region of a diseased appendix was the most probable cause of the obstruction which allowed the fecal impaction to occur.

### CONCLUSIONS

Hygroscopic gum laxatives must be given with caution if any disease is present in the bowel which might facilitate obstruction.

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## Xerostomia Successfully Treated with Nicotinic Acid\*

By

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**X**EROSTOMIA, also known as aptyalism, asalia or stomatitis sicca is a condition characterized by abnormal dryness of the mouth. The normal moist, smooth surface of the lining membrane of mouth, tongue and buccal regions is replaced by a dry, rough surface showing numerous cracks and fissures which bleed easily. This painful condition prevents the patient from eating and chewing properly, and, therefore, leads to early inanition and cachexia.

In general, the literature on xerostomia is meager. The disease was first described and named by Sir Jonathan Hutchinson in 1888 (1). By 1922 there were 47 cases reported (2) and by 1932, 60 cases (3).

The etiology of the disease is not clear in many instances. Dehydrating diseases such as diabetes mellitus and insipidus, high fever and diarrhea, may produce abnormal dryness of mouth, but should not be confused with true idiopathic xerostomia.

The literature enumerates the following causes in the etiology of the disease: atrophy, hypoplasia or fibrosis (Mikulicz' disease) of the salivary glands; lesions of the central nervous system, such as result from an injury to the head; lesions of the peripheral nerves supplying the salivary glands; psychogenic factors or mental shock, senile atrophic changes (4, 5, 6), X-ray treatment for facial hypertrichosis (7). In one of two cases, in which xerostomia was found to be associated with xerophthalmia the possibility of an avitaminosis A was suggested (5). A deficient diet as an etiologic factor is considered by Chamberlin (2). With the increased interest in vitamin deficiency diseases in recent years, lesions of the oral cavity, gingivitis, stomatitis, cheilitis, have been reported to be

due to avitaminosis. (8 Sydenstricker). In view of the rarity of xerostomia such relationship has not been demonstrated as yet. It is the purpose of this communication to report a case of xerostomia in whom an etiologic relationship to Vitamin B deficiency could be established.

### REPORT OF A CASE

Mrs. L. S., aged 49, was admitted to the metabolic clinic on June 17, 1938, with the essential complaints of xerostomia. Since 1930 the patient had noted a progressively increasing dryness of the mouth. At the time of admission the mouth was so dry and painful that she frequently had to sip water in order to keep the mucus surface somewhat moist. She had lost considerable weight and appeared emaciated. Physical examination revealed the dryness of the mouth extending over the whole oral cavity. The mucous membrane was completely dry and rough, showing numerous cracks and fissures. The mucous membranes of nasal cavities and of the conjunctival sac appeared to be normal and moist. There was no local pathology as to teeth and salivary glands. An X-ray lipoidal filling examination of the salivary glands revealed normal conditions.

There were no significant physical findings. A careful examination for possible evidence of other Vitamin B deficiency symptoms such as dermatitis, peripheral neuritis, gastro-intestinal symptoms, diarrhea and beriberi heart was negative. A gastroscopic examination and Ewald test revealed no abnormalities.

In view of the failure of previous medication it was thought justified to make a therapeutic attempt with Vitamin B. Inasmuch as it was not known a priori which fraction of the Vitamin B complex if any may be responsible for the xerostomia the patient was given yeast, thiamin chloride and nicotinic acid in fairly large doses.

The result was quite striking. When the patient was seen two weeks later, there was considerable moisture

\*From the Metabolic Clinic, Michael Reese Hospital, Chicago, Ill.  
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present in the oral cavity and the patient felt considerably relieved. It then was determined which Vitamin B fraction was responsible for the improvement. When yeast and thiamin chloride was given alone, the condition became rapidly worse but when nicotinic acid was added, the improvement was maintained. It was finally found that nicotinic acid alone in doses of 50 mgm. t.i.d. was capable of maintaining the patient free from xerostomia.

On the basis of our therapeutic test the conclusion seems justified that the xerostomia in this case was due to nicotinic acid deficiency. Further proof would require the demonstration of a diminished nicotinic acid level of the blood. However, the present laboratory methods are difficult technically and have not yet been used enough on normal cases to establish normal values.

I am unable to explain why the patient should have developed such a deficiency in nicotinic acid and if so why she should not have shown other symptoms of nicotinic acid deficiency, particularly symptoms of pellegra. It is certain that food rich in Vitamin B was available to our patient, however, it is conceivable that following a non-specific stomatitis or the extraction of teeth, etc., the vitamin intake may have been diminished to such an extent as to produce vitamin deficiency and xerostomia. This in turn may have prevented the patient from further

proper food intake and thus a vicious circle was established leading to the clinical picture described.

## CONCLUSIONS

1. The etiology of xerostomia has remained obscure in spite of numerous theories advanced.
2. A marked curative effect was obtained with nicotinic acid in a case of xerostomia of long standing.
3. Nicotinic acid deficiency should be included in the etiologic considerations of xerostomia.

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# Editorials

## THE EFFECTS OF ADSORBENTS ON INTESTINAL MOTILITY

**I**N the Proceedings of the American Society for Pharmacology and Experimental Therapeutics, Thirtieth Meeting, April, 1939, J. L. Morrison reported a study of the degree to which the several intestinal adsorbents commonly used at present might affect the rate of passage of food through the bowel.

White rats were fed measured portions of the materials and were killed an hour later. The whole intestine was then removed and its length measured. The distance traversed by the adsorbent from the pylorus in the unit of time was expressed as a percentage of the length of the bowel. Thirty rats were used for the study of each adsorbent.

One gram of food traversed 71 per cent of the tract, whereas bismuth subcarbonate, Lloyd's reagent, kaolin, calcium carbonate, barium sulfate, magnesium trisilicate, activated charcoal, and 7 per cent colloidal aluminum hydroxide, all went through with about the same, delayed, rate. The distance traversed ranged between 54 and 61 per cent of the intestinal length.

W. C. A.

## CARCINOMA OF THE DUODENUM

**A**S every gastro-enterologist knows, carcinoma of the duodenal mucosa is an extremely rare disease. In thousands of necropsies, we cannot remember having seen a case in which cancer appeared to have begun in a duodenal ulcer.

Usually, carcinoma of the stomach has difficulty in growing into the duodenal mucosa. It may grow down over the pylorus and into the peritoneal and muscular coat of the duodenum, but it will tend to leave the mucosa alone. Usually, when carcinoma invades the duodenum, it seems to come from the ducts of the pancreas and liver.

Years ago, Alvarez and Starkweather (1918) while studying the oxidative processes of the mucous mem-

brane in different parts of the digestive tract, found a remarkable difference in the catalase content of the mucosa on the two sides of the pyloric line. Orad to this line the catalase content was low and caudad to the line there was the highest catalase content found in any part of the digestive tract. This suggested the presence of a high metabolic rate in the duodenum. It is conceivable that a high rate of metabolism could have something to do with the high degree of immunity of the duodenal mucosa to carcinomatous degeneration.

In the Annals of Surgery for March, 1939, Lieber, Stewart and Lung presented a fine statistical study of carcinoma of the duodenum. They reported thirteen cases of their own and one from the literature. These were found during the making of 22,152 necropsies.

W. C. A.

## THE QUANTITY OF BLOOD REQUIRED TO PRODUCE A TARRY STOOL

**O**CCASIONALLY the gastro-enterologist will wonder how much blood must flow from the gastric or duodenal mucosa to produce a tarry stool. To answer this question, W. A. Daniel and Sherman Egan, under the direction of A. C. Ivy, gave varying amounts of blood to ten healthy medical students who were on a general diet and found that from 50 to 80 cc. of blood must come down the bowel to produce a tarry stool.

Often the physician will wonder how much significance to place in the patient's story of tarry stools, and sometimes, by paying too much attention to such a history, he will diagnose an ulcer when none was present. Occasionally, the dark stool will have been produced by the taking of bismuth or perhaps certain foods or medicines.

The wise clinician can generally tell whether or not a history of supposed melena is significant simply by asking the patient if, at the time the dark stools were

noticed, he was weakened, and if the stools were soft and foul smelling. With a hemorrhage of any size the patient usually feels a certain amount of shock and much weakness in the legs. Sometimes he will have difficulty in getting to or from the bathroom. After a good-sized hemorrhage he is likely to feel so weak that he will be glad to spend some time in bed. One must look with doubt on a history of dark stools if the patient was able to go on cheerfully with his work.

W. C. A.

#### THE INABILITY TO PRODUCE A HYPER-CHROMIC ANEMIA IN MONKEYS BY REMOVING THE STOMACH

IN the December, 1939, number of the "Annals of Internal Medicine," R. A. Bussabarger, A. C. Ivy, F. D. Gunn and J. S. Wigodsky reported on the blood changes seen after the removal of the entire stomach from eight young *Macacus rhesus* monkeys (five females and three males). Five of the animals survived for periods of time ranging from 478 to 937 days. None of them developed the blood picture of pernicious anemia. These negative results agree with those of Goldhamer who, in similar experiments, obtained only a secondary type of anemia. In Ivy's laboratory a further effort was made to produce pernicious anemia in the monkeys with the help of the highly deficient Wills diet, but without success.

Many experimenters have removed the entire stomach from a number of different species of adult animal, namely dog, cat, rat, pig and monkey, but with the possible exceptions of the rat and pig, none of the animals developed pernicious anemia. Unfortunately, a good deal needs yet to be learned about the etiology of this disease.

According to Petri, Norgaard and Bandier (*Acta Med. Scandinav.*, 98:117-127, 1938) some young dogs and pigs deprived of the stomach developed a fatal pellagra which was relieved by the giving of human gastric juice or dried hog stomach and not by the giving of nicotinic acid or yeast. In view of the less spectacular results obtained by other workers this report will have to be confirmed by further work before it can be fully accepted.

W. C. A.

#### THE RELATION BETWEEN THE HISTOLOGIC STRUCTURE OF CARCINOMAS OF THE STOMACH AND GASTRIC SECRETION

IN the December, 1939, number of the "Annals of Internal Medicine," Alexander Brunschwig and T. Howard Clarke reported an interesting study on the relation between the histologic structure of gastric carcinomas and the degree of gastric acidity associated with the lesion. Obviously, such a study is difficult because much must depend on the size and age of the lesion and on the amount of associated gastritis. The age of the patient should also be a factor.

In twenty-eight of the achlorhydric stomachs, the authors found the average size of the lesion to be 42 sq. cm. In six of eight stomachs showing hypochlorhydria, the average size of the lesion was 24 sq. cm., and in sixteen stomachs with a normal type of secretion, the average size of the lesion was 21 sq. cm. At first glance it would seem, then, that there is a relationship between size of the tumor and loss of gastric secretion. However, of the twenty-eight achlorhydric

stomachs, twelve contained lesions varying in size from 6 to 24 sq. cm., with an average of 14.8 sq. cm., and in the group of sixteen stomachs with normal secretion, five held lesions varying from 16 to 80 sq. cm. in size, with an average of 49 sq. cm.

In fifty-two cases, the location of the lesion in the stomach was compared with the gastric secretion, but no close relation could be found, unless, perhaps, the lesions around the pylorus were more frequently associated with achlorhydria. This might be due to the gastric stasis often associated with prepyloric lesions.

In sixty-eight cases, the lesions were classified in four groups of adenocarcinoma, medullary carcinoma, gelatinous carcinoma, and scirrhus carcinoma. In the first three groups, there was no evidence to indicate a relation between type of cell and quality of secretion. In the fourth group of six cases, there were five with normal secretion and one with hypochlorhydria. This may well have been due to the fact that often the scirrhus carcinoma grows largely in the submucosa and in the muscular coat.

We have long wondered why histologists do not make a great effort to identify the several carcinomas of the stomach as originating in the several types of cells found in the mucosa. One can easily see how the mucus-containing, or wrongly called colloid carcinoma, might originate in the mucus-forming "neck-chief cells." Some of the flat leaf-like cancers which grow widely on the surface of the gastric mucosa might grow from the flat epithelium that lines the mouths of the tubules. Theoretically some cancers should arise in the parietal or acid-forming cells, and such cancers might be associated with normal acidity. Another type of cancer might arise in the chief, or pepsin-producing cells. Such cancer cells might contain a propepsin. Perhaps if looked for, some explanation could be found for the fact that the scirrhus carcinomas tend to grow through the whole wall of the stomach as well as through the mucosa.

W. C. A.

#### IS THE BIOPHOTOMETER READING A TRUE INDEX OF THE AMOUNT OF VITAMIN A IN A PERSON'S BODY?

IT has long seemed to us that the men who brought out the biophotometer test for Vitamin A in the body were hardly justified in the speed with which they assumed that their method of measurement was correct and their arbitrary standards of normal acceptable. Surely they should have suspected that their standards were too high when three out of four American school children failed to come up to them.

We were much interested, therefore, to find an article by Steininger and Roberts in the December, 1939, number of "Archives of Internal Medicine" in which the authors went into the subject critically. They stated that of eight groups of workers who have reported on the use of the biophotometer, two confirmed the findings of Jeans and his associates, three gave somewhat qualified confirmation, and two of the three who did the most extensive and most carefully controlled work concluded that the machine is unreliable and the method of doubtful value.

Steininger and Roberts reported on the results of more than 2,000 biophotometer tests of 459 persons. They found that:

1. Single tests cannot be trusted because in some cases several successive readings will vary widely in



JOHN D. D.  
JULY, 1940

spite of the fact that the person has not altered his diet in the meantime. Usually, however, the readings are fairly constant.

2. Although children from a high socio-economic level generally have a better light adaptation than do children from a low socio-economic level, *only 26 per cent* of the children in the presumably well-fed group gave readings which are regarded by Jeans as normal. On the face of this it would seem that his standards must be wrong. Seventy-four per cent of the children of fairly well-to-do people in the United States with all their easy access to milk, cream and butter can hardly be suffering from malnutrition. If *they* are in a bad way, how on earth do the children of the poor keep alive in the Orient where they live on so little that growth is stunted, and where they never get milk, cream or butter or a supplemental feeding of Vitamin A? Actually, what most of our American dietitians have needed badly for years, in order to keep sane, has been a trip to the Orient—to China, Japan and India, where the average man lives on a few dollars a year.

3. When a supplementary feeding was given to fifty children who were found to have a poor adaptation to light, more than half of them failed to show any improvement, and one out of four of the children used as controls, who didn't get any supplementary feeding, gained more in light adaptation than did those who were stuffed with Vitamin A!

4. A diet low in Vitamin A caused a significant change in the biophotometer readings in only two out of six subjects, although some were kept on the diet for four months!

At the sixteenth annual conference of the Milbank Memorial Fund (1938), Hecht reported the designing of a new biophotometer with which he believed more satisfactory measurements could be made. He found that when a person went on a diet deficient in Vitamin A there was a fairly rapid loss in retinal adaptation to darkness. With the change to a good diet with supplemental Vitamin A the return to normal adaptation was slow. One trouble with the test is that certain diseases such as cirrhosis of the liver which interfere with the passage of Vitamin A from the bowel to the tissues can cause a big loss in speed of adaptation to darkness in spite of the fact that the patient is on an adequate diet.

In the next paper in the symposium Feldman admitted that the results of the testing might vary with the skill of the technician. He found that a defective adaptation could be produced by several chronic diseases, including arteriosclerosis, hypertension, and toxic goiter.

In the discussion Dr. C. E. Palmer stated that he and his associates had studied 500 children with the biophotometer and had been unable to confirm Jeans' work. One hundred of the children adapted slowly in spite of the fact that their diet did not seem to be deficient. These children were divided into two groups of fifty, one receiving extra Vitamin A and the other similarly appearing capsules containing mineral oil. At the end of eight weeks the adaptation to light had improved greatly in *both groups*! The children apparently had become accustomed to the machine. Dr. Charles Snelling of Toronto, also reported discordant results obtained with both Jeans' old and his new photometer.

All these results make it evident that although a relation often exists between the speed of adaptation to darkness and the state of nutrition as regards Vitamin A, the relation is not perfect enough to warrant the uncritical assumption that a low photometer reading means the presence of an asymptomatic Vitamin A deficiency.

According to Torstein Lindquist whose book on Vitamin A in man was reviewed in the Journal of the A. M. A. for July, 1939 (page 257), there isn't a perfect correlation between the amount of night blindness and the amount of carotenoids and Vitamin A in the blood serum. Patients with night blindness had from 40 to 239 units of A in 100 cc. of serum, while persons with a good adaptation to light had from 69 to 548 units. Obviously there is much overlapping of the distributions of the two sets of data.

We have here, then, an example of the common curse of modern medical literature. Much work is done at first without sufficient controls and the early reports are too enthusiastic. A few years ago Vitamin A was said to be the important factor in protecting mucous membranes from infection, but as soon as a number of investigators in several parts of the world studied the problem with proper controls, it was found that children on a Vitamin A poor diet had no more respiratory infections than did those on a diet rich in Vitamin A.

Today in many institutions patients with ulcer are being told that they must stuff themselves with vitamins. If there is any evidence back of this injunction, we haven't yet seen it. What bothers us is that the therapeutic experiment is being carried out in such a way that in a hundred years no conclusive evidence can be obtained for or against the procedure.

The trouble with us physicians is that when a new therapeutic idea comes to us we use it on every patient. We remove teeth from every patient, we give a high Vitamin diet to every patient, or we give sulfanilamide to every patient with an infection. As a result, when later we are ready to change to a new fad, we usually haven't the slightest information as to which patients can be benefited by the old treatment and which are likely to go on with the disease unchanged. After going after focal infections vigorously and fanatically for thirty years, how many of us could go before a meeting of, let us say, the Harvey Society, and present a clear statement to show which types of arthritis are helped by the removal of foci and which are not? If only we would treat *half our patients* with the new method and keep the other half as a control group on some old method, we might learn something.

There is a great need also for the prompt reporting of toxic and unfavorable results obtained with new drugs. The introducers of these drugs always seem to have a blind spot for the bad reactions. All physicians should read the reports made recently to the Council on Pharmacy and Chemistry of the American Medical Association by several groups of men who tried out Stilbestrol (J. A. M. A., December 23, 1939). Some found it so toxic in more than half of the cases that they could hardly use it, while others didn't seem to notice much trouble with it. The reader is forced to conclude that many physicians are accustomed to turning a deaf ear to the complaints of patients who,



when they try a new drug, vomit or become toxic, dis-oriented, or even jaundiced and seriously ill.

W. C. A.

## THE ABILITY OF MAN TO EAT BROKEN GLASS

**E**SPECIALLY during the spy scares of the first World War, many persons feared that they might be poisoned by having ground glass put into their food. At that time, several medical authorities doubted if such glass could do any great harm.

In the Journal of the American Medical Association for December 23, 1939, page 2341, it is pointed out that in edition 2 of the textbook on "Legal Medicine and Toxicology," edited by Peterson, Haines and Webster, volume II, pages 888-897, a case is reported in which a professional glass-eater ate half a dozen 6-inch test tubes, two good sized lamp chimneys, a 4-ounce medicine bottle, two small pieces of window glass, and three small pieces of colored glass. In the presence of Drs. Haines and Ingals, the man bit off pieces, chewed them and swallowed them just as one would deal with ordinary articles of food. He had first eaten a hearty meal, as was his custom before one of his performances.

At the time, he didn't show any discomfort, but some two or three years later he died, possibly from irritation of the digestive tract produced by his long-continued glass-eating. Apparently there have been a number of other such glass-eaters whose activities have been observed by scientific men.

Years ago a man named Exner wrote of a reflex by which the bowel tends to relax when the mucous membrane is pricked by a sharp body. This has since been known as Exner's reflex, but its presence hasn't been well confirmed by physiologists, and the mechanism by which sharp foreign bodies, such as pins and needles, get through the intestine is not really understood. We remember once seeing a cat at necropsy with a piece of large fish hook half way through the

wall of the stomach on the lesser curvature side. Apparently this had been present for some time. The gastric wall had gripped the shank of the fishhook (about 4 mm. in diameter) so firmly that there was little if any leakage of gastric juice.

W. C. A.

## THE SYMPTOMS OF GIARDIASIS

**F**OR years, some authorities have claimed that *Giardia intestinalis* is a harmless saprophyte. We have always doubted this, because we have seen several patients with a heavy infestation who recovered instantly and miraculously after one intravenous injection of neosalvarsan, which temporarily killed off the organisms.

In one case, a nurse who for a year had been too miserable to work, felt like going on duty the day after the treatment. It didn't seem possible that this improvement could have been due to psychotherapy, because the physician had had no great hope of helping her and had not promised any relief.

In the "Acta medica Scandinavica," Stockholm, for March 9, 1939, P. de Muro reported his experience with forty-five cases of giardiasis. He believed the symptoms could be classified as those of enterocolitis, rectocolitis, pancreatic insufficiency, and some sort of hepatobiliary disturbance. In most cases, the enterocolitis type of picture was the one presented. The symptoms were similar to those of amebiasis. According to de Muro, some of the patients presented nervous disturbances associated with the intestinal distress. Muro believed that with chronic giardiasis there often exists some pancreatic insufficiency. Sometimes the stools are soft and mushy, but at other times the patient will be constipated. Many patients complain of asthenia.

Fortunately, most observers agree now that atabrine is a splendid drug in these cases, and it would seem wise, whenever this infestation is found, to clear it up.

W. C. A.

## Abstracts of Current Literature

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WALTHER, G.

*Kohlenmonoxydvergiftung und Magensaftsekretion.*  
Arch. exp. Path. u. Pharmacol., 192(3):361-371, 3 figs., 1939.

Gastric acidity was detd. in rabbits poisoned with CO. Both acute and repeated intoxication were studied. 1-7 treatments with CO did not usually alter gastric acid secretion, occasionally it raised, occasionally lowered the acid secretion; the form of curve was not altered. Mucus secretion often increased slightly. Achlorhydria was not observed after either single or repeated poisonings. Histologically in acute poisoning, hemorrhagic erosions of the stomach wall were seen, with leucocytic infiltrations of the borders. Villi tip oedema was evident, hyperemia, mild

inflammatory oedematous saturation of the upper mucosa layers, necroses and leucocytic infiltrations in the mucosa. In animals chronically poisoned with allyl formate and repeated CO treatments, occasionally lower gastric acid values were obtained but never achlorhydria. After 3-4 months of the combined intoxication, connective tissue increased in the mucosa, the villi tips showed hyperplasia, etat mamellone, and irregularities of the gland picture. The changes corresponded to the picture of an atrophic-hyperplastic gastritis, not throughout the stomach, but in localized areas. In the antrum epithelium changes occurred; formation of indifferent epithelium in Moczkowicz's terminology. All the effects could be ascribed chiefly to chronic allyl formate intoxication. The question whether

or not CO alone could cause similar pathology was discussed. In animals with secondary anaemia CO did not alter the gastric acid secretion.—C. S. Leonard (Courtesy of Biol. Abst.).

BRESE, B. B. AND MCCOORD, AUGUSTA B.

*Vitamin A Absorption in Celiac Disease. J. Pediatrics, 15(2):183-196, 1939.*

Ten cases of celiac disease, one of suspected cystic fibrosis of the pancreas, and 48 cases with other complaints were studied from the standpoint of ability to absorb Vitamin A from the intestine. After first taking a basal blood specimen, each patient was given Vitamin A as fish liver oil in the amount of 7,000 U.S.P. units per kg. of body weight. Blood specimens obtained at 2, 4, 6, 9, 12 and 24 hours after the adm. of the oil were then studied by the colorimetric method of Carr and Price. In the 10 cases of celiac disease, the fasting Vitamin A content of the blood was low, and after treatment, this level rose but the ability to absorb Vitamin A was still markedly below that of the controls. Treatment with a high protein, low fat and carbohydrate diet modifies but does not alter the inability of the intestine in coeliac disease to absorb Vitamin A. This deficiency was even more marked in the case of suspected fibrosis of the pancreas. The 48 control cases were unaffected.—N. H. Einhorn (Courtesy of Biol. Abst.).

LIUM, R. AND FLOREY, H. W.

*The Action of Magnesium Sulphate on the Intestine of the Cat. Quart. J. Exp. Physiol., 29(3):303-312, 1939.*

Isotonic  $MgSO_4$  slows the absorption of isotonic NaCl solns. in the intestine of the cat. It does not influence the absorption of glucose solns. It does delay slightly the absorption of distilled water. Isotonic  $MgSO_4$  is no more irritating to the colon than isotonic NaCl as evidenced by histological studies. Its action in producing purgation is probably that of diminishing absorption and thereby producing mechanical stimulation for defecation by the increased bulk.  $MgSO_4$  in small doses produces loose and watery stools in cats for several days. This may be due to its effect in slowing the absorption of other crystalloids. Solns. of NaCl are best absorbed from the ileum; of glucose, best from the jejunum in cats. Decapitate cats cannot be considered to be completely normal with regard to intestinal motility. Washing and excessive handling of the colon tend to make it irritable and give inconsistent results in acute expts.—H. W. Florey (Courtesy of Biol. Abst.).

RUFFIN, JULIAN M. AND MACDONALD, DICK.

*The Significance of Gastric Acidity After Histamine Stimulation: A Statistical Study of 2877 Gastric Analyses. Ann. Internal Med., 12(12):1940-1947, 1939.*

The acid values of 2877 patients were studied (1917 of these showed no evidence of disease). The range of gastric acidity in the normal individual was found so great when histamine was used that it was impossible to determine what values were to be taken as evidence of normal acidity, hyper- or hypoactivity; this range was much greater after histamine than after the Ewald meal; if free HCl was present after histamine stimulation, the actual level of acidity was of little, if any, diagnostic significance. However, the demonstration of achlorhydria in a patient was of sufficient importance to justify the procedure.—M. L. Hsley (Courtesy of Biol. Abst.).

NEW, GORDON B. AND HERTZ, CHARLES S.

*Malignant Disease of the Face, Mouth, Pharynx and Larynx in the First Three Decades of Life. S. G. O., 70:2-163, Feb. 1, 1940.*

This report covers 233 patients with malignant disease of the face, mouth, antrum, pharynx and larynx. It was interesting to note that 33 males and 30 females were under

20, while the number between 20 and 30 increased to 107 males and 63 females. There was a high percentage of survival without recurrence for 5 and 10 years after treatment. Twelve per cent of the lesions were sarcomas and 88 per cent were carcinomas. The changes for recovery are much greater for the latter type.

In squamous cell epithelioma, the grade of the malignancy is important since Grade 1 offers a 90 per cent chance for survival five years or more, while Grade 4 offers a 3.8 per cent hope for survival. Patients with basal cell and combined basal cell and squamous cell epithelioma of Grade 1 have a 100 per cent chance for five year survival.

According to this record, the chances for at least 5 years' life after treatment are greater than is ordinarily expected. Patients with malignant diseases of the tongue, palate, tonsil, pharynx, upper jaw and antrum, lower jaw and larynx, including patients with cancers of the lip have a chance of from 30 per cent to 55 per cent for 10 years' survival after treatment.—Francis D. Murphy.

MINIBECK, H.

*Die Selektive Zuckerresorption beim Kaltblüter und ihre Beeinflussung durch Nebennieren- und Hypophysenextirpation. Pflügers Arch. ges. Physiol., 242(3):344-353, 1939.*

During narcosis (urethane or ether), the duodenum of big Hungarian frogs were ligated at the pyloric and at the colic end, and then injected with 1 cc. of isotonic solns. of various sugars. After closing the abdominal wall and the skin, the frogs were kept for 8 hours in glass vessels, then sacrificed, and the duodenum dissected and its content carefully collected and analyzed for the various sugars according to the methods of Hagedorn-Jensen. A selective resorption existed for glucose and galactose; this disappeared from the duodenum 3 or 4 times more quickly than did that of fructose, mannose, sorbose, and xylose. After adrenalectomy or hypophysectomy (ant. lobe) this selective resorption for glucose and galactose was absent. All sugars were absorbed with the same speed, corresponding to that observed for fructose, etc., in normal frogs. The author assumed an influence of the ant. lobe of the pituitary upon the cortex of the adrenals. — E. Fischer (Courtesy of Biol. Abst.).

EADES, CHARLES C.: *The Treatment of Carcinoma of the Colon in Small Hospitals. S. G. O., 70:3-711, March, 1940.*

This study reveals the end-results of patients with carcinoma of the large bowel who were treated in a small general hospital. Forty-nine patients were treated over a 10 year period by 11 different surgeons.

The author stresses the importance of pre-operative care. Economic factors enter into the picture and patients are usually reluctant to spend more than three or four days in the hospital before operation is performed or they may procrastinate operation because of the cost. The author feels that proper pre-operative management of non-surgical decompression maneuvers with the Wangenstein apparatus or the Abbott-Johnson intestinal tube in acute intestinal obstruction would lower the mortality rate. The water balance should be established in these dehydrated patients; the chloride level can be brought to normal by administration of  $\frac{1}{2}$  gram of sodium chloride per kilogram of body weight for each 100 milligrams that the blood plasma chloride level has been depressed. Blood transfusions should be used before operation.

It is the author's belief that the low mortality statistics of large clinical centers are the direct result of specialized management. For better results in a small hospital, a qualified surgeon particularly interested in colon surgery should be allowed to supervise the treatment of all patients with cancer of the colon.—Francis D. Murphy.

MARSHALL, SAMUEL F.

*Regional Ileitis. New England J. of Med., 222:375-382, 1940.*

The article is a report of forty-eight cases observed at the Lahey Clinic during the past six years. Twenty-nine were confirmed by operation. In sixteen instances the ileocecal junction was involved, in three cases the cecum and ileum, in ten cases the ileum alone. In two instances upper loops of ileum or jejunum were involved. In two other cases most of the ileum and a part of the jejunum was involved.

Perforation occurred in three cases with formation of an abscess in the right lower quadrant. One case perforated into the sigmoid, another into the urinary bladder and two others into the ascending colon.

In seven cases fistulas following appendectomies was the initial complaint.

Even though spontaneous remission occurs the author states that the method of treatment is surgical. He feels however, that operation during the acute phases should be avoided in order to prevent resultant fistulas.

The surgical procedure advocated is the two stage Miculicz resection removing a portion of the cecum and ascending colon along with the terminal ileum. In two of the cases recurrence occurred which the author feels may have been due to skipped areas.—Henry H. Lerner, Boston, Mass.

#### *Gastroscopy—An Aid to Diagnosis of Pancreatic Carcinoma.*

The diagnosis of carcinoma of the pancreas is at most based upon indirect evidence. Even in the presence of typical signs and symptoms the diagnosis can only be definitely determined by surgical intervention. Pre-operative differential diagnosis is seldom accomplished. The common opinion may be stated that carcinoma of the pancreas can not be diagnosed early.

Moersch and Comfort, in the November, 1939, issue of the American Journal of Surgery, reported two cases in which gastroscopy served as an aid in the diagnosis of carcinoma of the pancreas. This sign, which consisted of a bulging inward of the posterior wall of the stomach as seen with the gastroscope, led to a correct diagnosis in two of their cases.

Realizing that this added diagnostic procedure might be of value, a third case is reported here. The patient was a sixty-two year old male with a seven weeks history of dull gnawing epigastric pain, not relieved by food or alkalies, but made worse with meals. During this seven weeks period there had been a loss of twenty pounds of weight. On admission to the hospital examination showed a mass in the mid abdomen. Gastric analysis showed an absence of acid and the presence of blood in every specimen. X-rays were reported as showing a deformity involving the antrum of the stomach. Whether the mass was intrinsic or extrinsic could not be determined. To determine this gastroscopy was performed. Complete visualization of the interior of the stomach could not be obtained because of what appeared to be a mass pushing forward the posterior wall. The mucosa overlying this area appeared normal. Because of this a diagnosis of a mass in the retroperitoneal space was considered. Autopsy later revealed a carcinoma of the pancreas with extension into the stomach.

This case is reported in the hopes that other cases in which malignancy of the pancreas is suspected will be subjected to gastroscopy. If this procedure increases our ability to diagnose pancreatic carcinoma more frequently and earlier, it will add another weapon to our diagnostic equipment.—Henry H. Lerner, Boston, Mass.

FERRIMAN, DAVID.

*Results of Ambulant Treatment of Peptic Ulcers. British Med. J., 1:210-211, Feb. 10, 1940.*

Ferriman reports on the curative value of the ambulatory treatment in 42 cases of uncomplicated gastric and

duodenal ulceration. The patients were placed on a diet excluding red meats, spices, alcohol and restriction of cigarettes, with six meals. Medication was given only when needed; alkalies (magnesium carbonate and bismuth oxy-carbonate) for pain; some were given bromide and phenobarbitone. Tr. belladonna was given to half of the patients.

Radiographic examinations were made every three months and continued for some time after the disappearance of the ulcer. Those cases which showed little or no healing at the end of a year, were considered failures. In 39 of the 42 cases, there were 23 successes, 7 failures, and in 9 the data was incomplete. Cures constituted approximately 75 per cent. Ferriman points out that absolute proof of healing is furnished only by gastroscopy, and that the gastroscope has shown that disappearance of radiological signs of an ulcer indicates considerable but not necessarily complete healing. The same applies to occult blood findings.—Maurice Feldman, Baltimore, Md.

SENTURIA, HYMAN R.

*Gastric Neurinoma. Am. J. of Roent. and Radium Therapy, Vol. XLIII, pp. 61-65, No. 1, Jan., 1940.*

During the last years several cases of neurinoma of the stomach were described. Senturia emphasizes that the roentgenological findings are very characteristic to permit an accurate diagnosis. Classically this is an oval to round, smoothly outlined defect with an "en face" niche, usually located on the posterior wall of the stomach, leaving the curvatures regular and undisturbed. These cases show larger hemorrhage either in the form of melena or hematemesis. These tumors are soft, elastic, were circumscribed, spherical, often lobulated. They are usually single covered by mucous membrane which is very vascular and may be thickened, and may or may not be ulcerated. Microscopically the picture is very characteristic in the palisade arrangement of the elongated nuclei. Most cases are benign although malignant transformation has been recorded.—Franz J. Lust.

MCPEAK, C. N.

*Benign Duodeno-Colic Fistula. Radiology, 34:343, March, 1940.*

The author reviewed the literature and presented two instances of this rare condition. The presence of the lesion was proved at operation in both cases and by necropsy in one. This benign fistula is usually the result of perforation of a duodenal ulcer into the transverse colon. The fistula is demonstrated by barium enema, and may be missed by barium meal studies. The benign origin of the fistula may be suspected from its appearance on roentgen examination, but an exploratory operation is essential in order to exclude the presence of a malignant lesion.—Robert Turell.

SNYDER, R. G.

*The Value of Colonic Irrigations in Counter-acting Auto-intoxication of Intestinal Origin. Med. Clin. of North America, N. Y. Number, pp. 781-788, May, 1939.*

Snyder discusses the very important topic of colonic irrigations and its value in counter-acting auto-intoxication. The symptoms of auto-intoxication are mostly clinical as apparently little is known of the absorption of toxic and infectious material from the colon. Most of the patients complain of drowsiness, dizziness, mental depression, inability to concentrate and headaches. Sometimes these patients complain of low grade fever, abdominal distention, eructations, flatulence, nausea and vomiting. The roentgenological examination demonstrates dilatation of the ileum with slow progress of the contrast substance, and a large amount of fecal content throughout the colon is found. Very often there is redundancy of the colon present. Occasionally diverticula are seen. The size and

volume of the colon are frequently out of proportion to the stature of the patient.

Snyder uses the "long tube method," which he thinks is more beneficial because of the additional mechanical stimulating effect of the tube upon the bowel wall. In none of his cases, which were examined proctoscopically, was irritation to be found in spite of the 10 to 20 irrigations at 2 or 3 day intervals. Among the interesting findings was the beneficial result of colonic irrigation in cases of obstruction of the sigmoid due to diverticulitis of the sigmoid with spasm.—Franz J. Lust.

KORNBLUM, K. AND FISHER, L. C.

*Carcinoma as a Complication of Achalasia of the Cardia.* *Am. J. Roent.*, 43:364-376, March, 1940.

The authors discuss the cause and incidence of achalasia and the occurrence of carcinoma with achalasia based upon hyperplasia resulting from small wart-like nodules or papillomata which may subsequently become malignant.

Mention is made of the incidence in Gottstein's series of 33 cases of achalasia in which 3 were carcinomatous; and Rake's 15 pathological specimens of achalasia with 3 malignancies.

Kornblum and Fisher report 4 cases of carcinoma of the esophagus with achalasia. They emphasize the importance of evacuating the contents of the dilated esophagus and the esophagoscopic examination in the diagnosis.—Maurice Feldman, Baltimore, Md.

HUBENY, M. J. AND POLLACK, S.

*Saccular Abdominal Aortic Aneurysm. An Analysis of 48 Cases.* *Am. J. Roent.*, 43:385-393, March, 1940.

The authors report three cases of abdominal aorta aneurysm, with illustrations demonstrating the roentgen signs of this condition. The etiology and symptoms are briefly discussed, with a review of 48 collected cases.

The following important diagnostic facts are brought out. In 5 of 8 cases in which preliminary films were made, calcifications were observed. A palpable mass found in 33 cases or 71 per cent. 30 of 32 cases with a mass had expansile pulsation. A soft tissue mass may be seen in the preliminary film. Erosion of the vertebra adjacent to the aneurysm and pressure signs on the gastro-intestinal organs are commonly observed. The authors cite Neely's incidence of 5 cases in a series of 1,385 autopsies.—Maurice Feldman, Baltimore, Md.

FOORD, A. G. AND BAISINGER, C. F.

*Comparison of Tests for Bilirubin in Urine.* *Am. J. Clin. Path.*, 10:238-244, March, 1940.

Foord and Baisinger describe the various methods utilized in tests for bilirubin in the urine. A brief discussion of the following tests are given, namely, Rosenbach's; Huppert-Nakayama; Müller direct method; Müller concentration method; Diazo-Hunter; Diazo Spot (Godfried); Harrison Spot (Godfried); Zins; Naumann; and Fellingner and Menkes. The authors emphasize that the Diazo Spot test developed by Godfried is most easily read and most sensitive; its only objection is the unstable Diazo mixture. However, they point out that in the barium chloride concentration test the reagents are stable.

They recommend the Diazo Spot method of Godfried, the Harrison Spot and the Naumann methods as highly satisfactory.—Maurice Feldman, Baltimore, Md.

HINKEL, C. L.

*Spontaneous Pneumoperitonium Without Demonstrable Visceral Perforation.* *Am. J. Roent.*, 43:377-382, March, 1940.

The author reports a case of spontaneous pneumoperitonium in a woman aged 70. Air was observed beneath both diaphragms. A gastro-intestinal and barium enema roentgen study and clinical investigation did not disclose

the source to explain the presence of free air in the peritoneal cavity.

The appearance of spontaneous pneumoperitonium usually indicates perforation of a viscus. However, it is believed that it is not pathognomonic. Hinkel discusses causes other than perforation which may produce pneumoperitonium, namely, air entering the peritoneal cavity from the use of a bulb syringe douche for vaginal cleansing; rupture of cysts in the case of pneumatosis cystoides intestinalis; complication of a pneumothorax; and the accidental insertion of the needle below the diaphragm in thoracentesis. He points out that only two other cases have been reported with spontaneous pneumoperitonium, without peritonitis and without demonstrable visceral perforation. These were by Moberg, and by Monod and Holiander.—Maurice Feldman, Baltimore, Md.

COPE, V. ZACHARY.

*Extra-abdominal Resection of the Colon.* *British Med. J.*, 1:143-145, Jan., 1940.

Cope is of the opinion that any lesion of the colon accompanied by obstruction, there was no procedure so likely to be followed with success as extra-abdominal resection, provided always that extreme distention had been overcome by a previous caecostomy or colostomy. He discusses a technic which he has developed, using a special crushing clamp with three blades. The bowel is divided by the cautery, after removing the middle blade. The two stumps are then laid side-by-side and sutured. Two special metal tubes are placed in the ends of the bowel; these are fitted into a metal gate which is approximated and pressed together by screw pressure. Each day thereafter the pressure is increased, until about the 5th or 6th day, the tubes finally came away, and about 10 or more days the opening was closed. He discussed Devine's method, but believes his method gives a larger resection.—Maurice Feldman, Baltimore, Md.

PALMER, WALTER LINCOLN AND NUTTER, PAUL B.

*Peptic Ulcer and Achlorhydria.* *Arch. Int. Med.*, Vol. 65, pp. 499-509, 1940.

In this paper, consideration is given to the question whether or not peptic ulcer occurs in the complete absence of acid gastric juice. In a previous communication, study of 1,000 cases of gastro-duodenal ulceration revealed that there was no conclusive evidence that chronic ulcer occurs in the complete absence of acid gastric juice. It was pointed out that before the diagnosis of ulcer with anacidity must be "histamine proved" and the ulcer must be shown not only to be present but to be not syphilitic, tuberculous or carcinomatous.

In the present study the authors admit that small acute and subacute gastric ulcers may occur in the presence of achlorhydria proved by the histamine test. Such superficial ulcers may be only 2-5 mm. in diameter, not seen by X-ray, and found gastroscopically only in the presence of a thin atrophic mucosa.

Such lesions do not become chronic nor are they of large size. Large chronic gastric ulcers occur only in the presence of acid gastric juice and therefore they conclude that acid gastric juice plays an essential role in the genesis and course of chronic gastric ulcer. In a series of over 2,200 cases of proved (X-ray, gastroscopy or operation) active gastric or duod. ulcer, no instance of complete and persistent achlorhydria has been encountered in the past 12 years.—Albert Cornell.

QUICK, A. J.

*The Clinical Application of the Hippuric Acid and the Prothrombin Tests.* *Am. J. Clin. Path.*, 10:222-233, March, 1940.

The author describes the oral and intravenous methods for hippuric acid test for liver function, and also the

method of determining quantitatively the prothrombin of the blood.

The hippuric acid test determines the synthesis of glycine and the conjugation of benzoic acid and glycine. The test gives the maximum functional capacity of the liver, since the organ is given more benzoic acid than it can convert into hippuric acid in the period of time allotted. He points out that one measures not only the output of work for ordinary physiological demands, but also the reserve. Quick concurs with Snell's emphasis on the fact that when a patient with biliary disease has an hippuric acid output of 50 per cent or less of normal, he is a poor operative risk. He points out, however, that a low hippuric acid output does not invariably denote damaged hepatic function. If normal it would seem justified that serious liver damage does not exist.

Quick emphasizes the value of the hippuric acid test in determining, (1) quantitative hepatic function, (2) aiding in the differential diagnosis, (3) evaluating therapy, (4) following progress, and (5) obtaining new information of physiology of the liver.

The author describes the method of determining quantitatively the prothrombin of the blood. He likewise points out that the liver plays an important rôle in the synthesis of prothrombin, and it is believed that the organ has an essential part in converting Vitamin K into the prothrombin component.—Maurice Feldman, Baltimore, Md.

KIRSHBAUM, J. D. AND POPPER, H.

*Toxic Hepatitis. Arch. Int. Med., Vol. 65, pp. 465-476, 1940.*

Acute yellow or red atrophy, the fatal form of toxic hepatitis, is characterized by a small atrophic liver with microscopic evidence of necrosis of liver cells. In the non-fatal type, of which so-called catarrhal jaundice is typical, the liver is usually enlarged. Since most patients recover, little is known of the pathologic changes in this form.

The authors describe a group of fifteen cases in which the jaundice was fatal, where the liver was found to be enlarged at autopsy, with a clinical picture of an acute fulminating liver disease, death occurring with a short time (average—9½ days), just as in cases of acute yellow atrophy. They consider this group as representing an intermediary stage between catarrhal jaundice and acute atrophy and point out that in severe parenchymatous jaundice such as this, the prognosis may be poor despite an enlarged liver. The enlargement is due to the presence of a protein-rich fluid between the liver cells or, really, an edema (due to capillary damage with subsequent loss of plasma protein). The increasing fluid between the cords of liver cells finally destroys their structure, leading to dissociation of the cells. The cellular damage accounts for the atrophy of the organ while the capillary damage explains the hepatomegaly. There is also central necrosis with heavy infiltration of fat and bile pigment. Although unable to make a positive statement as to the etiology, the authors assume the presence of a toxin, possibly due to food poisoning and other factors. The icterus is due to the necrosis of liver cells plus serous hepatitis (toxic edema of the liver).—Albert Cornell.

LEVY, HYMAN AND LICHTMAN, S. S.

*Clinical Characterization of Primary Carcinoma of the Body and Tail of the Pancreas. Arch. Int. Med., Vol. 65, pp. 607-626, 1940.*

Carcinomas of this portion of the pancreas are not a rarity, yet diagnosis is felt to be difficult because physical findings are commonly absent and the symptom complex is vague in many.

The authors observed 19 cases of carcinoma of the body and tail of the pancreas, proved by laparotomy or necropsy and have analyzed their observations so as to formulate more satisfactory diagnostic criteria. The symptom complexes are explained on the basis of actual neoplastic

invasion, local and distant metastases, or mechanical pressure. The following clinical signs and symptoms assume diagnostic significance: 1. Rapid weight loss—unaccounted for by diabetes, tuberculosis, hyperthyroidism, anorexia nervosa, sprue or demonstrable malignancy. 2. Anorexia. 3. Non-colic abdominal pain—either diffuse or in the upper portion radiating to the lumbar region, unrelated to the digestive cycle, unrelieved by food, often nocturnal and relieved by change in posture. 4. Absence of anemia. 5. Absence of occult blood in the stool (unless the tumor has invaded the stomach or duod.). 6. Disturbed carbohydrate tolerance—manifested by glycosuria, hyperglycemia, or a dextrose tolerance curve of the diabetic type. 7. Atypical X-ray findings in the stomach or duodenum. 8. Elevation of the blood amylase. 9. Hemorrhagic ascites. 10. Peripheral venous thrombosis.

The absence of secondary anemia and occult blood in the stool and presence of significant weight loss sharply differentiate these carcinomas from gastric carcinoma in which significant loss of weight is invariably coupled with secondary anemia and occult blood in stool. This group of pancreatic carcinomata may also simulate partial high gastro-intestinal obstruction with duodenal stasis, peptic ulcer, intra-abdominal suppuration.—Albert Cornell.

BLOOMFIELD, ARTHUR L.

*The Decrease of Gastric Secretion with Advancing Years: Further Observations. J. Clin. Invest., Jan., 1940.*

It is well known that gastric secretion decreases with advancing years. Whether this decrease is a gradual one or whether it occurs abruptly has been studied by means of repeated gastric expressions with histamine on the same individuals over a ten year period. Among five subjects reexamined after intervals of over ten years, three showed practically identical gastric secretion, one showed slight decline of acidity but not of volume of secretion and in one there had been a definite decline both of volume and of acid. The findings suggest that the fall in secretion found in large groups of people in the older age range must be the resultant of various types of change in different individuals. The author has also studied basal secretion in groups of people at various ages and finds that it declines with advancing years.—Charles A. Flood.

STEVENS, RICHARD J., SCHIFF, LEON, LUBLIN, ANNA AND GARBER, ELLEN S.

*Renal Function and the Azotemia Following Hematemesis. J. Clin. Invest., Jan., 1940.*

Elevation of the blood urea nitrogen following massive hemorrhage from the stomach or duodenum has been attributed to shock, dehydration, starvation, renal insufficiency and absorption of digestive products of blood in the intestinal tract. The authors have emphasized the importance of the latter factor. In four cases of massive gastro-intestinal hemorrhage, renal function tests were carried out. The urea, inulin and phenol red clearances were determined and found to be either normal or somewhat decreased. The decrease when present was not sufficient to account for the increased blood urea. Elevation in blood urea following hematemesis is not due to decreased renal function.—Charles A. Flood.

GUTMAN, ALEXANDER B., OLSON, KENNETH B., GUTMAN, ETHEL BENEDICT AND FLOOD, CHARLES A.

*Effect of Disease of the Liver and Biliary Tract Upon the Phosphatase Activity of the Serum. J. Clin. Invest., Jan., 1940.*

Serum phosphatase determinations were carried out in over 300 cases of disease of the liver and biliary tract. The determination is of real value in the differential diagnosis between obstructive jaundice due to calculus in the

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common bile duct or neoplasm and hepatogenous jaundice. In 90 per cent of the cases of obstructive jaundice in this series the serum phosphatase level exceeded 10 Bodansky units while in catarrhal jaundice the phosphatase level was less than 10 units in 90 per cent of the cases. In jaundice following arsphenamine, wide variation in the behaviour of the serum phosphatase occurs. An elevation in serum phosphatase was encountered frequently in secondary neoplasm of the liver with or without jaundice and the test is of some value in the early detection of liver metastasis in patients known to have malignancy. Liver abscess was usually associated with distinctly increased values. It is suggested that the determination be employed to complement other liver function tests and that it offers a sensitive criterion of the integrity of the excretory biliary passages.—Charles A. Flood.

ELSON, K. O'SHEA, LUKENS, FRANCES D. W., MONTGOMERY, ESTHER H. AND JONAS, LEON.

*Metabolic Disturbances in Experimental Human Vitamin B Deficiency. J. Clin. Invest., Jan., 1940.*

A normal individual was placed on a diet adequate except for the Vitamin B complex and observations were carried out on water balance and carbohydrate metabolism. Edema appeared early in the deficiency, and was not attributable to changes in serum protein. Increase in glucose tolerance and elevation in blood lactic acid took place but no increase in the bisulphite binding power or fasting pyruvic acid of the blood were found. After a period of more than two months on the deficient diet the individual was treated with thiamin chloride, followed later with riboflavin and finally by brewers yeast. The edema did not disappear until yeast was administered. The decreased glucose tolerance also was not corrected by treatment with thiamin chloride and riboflavin but disappeared after yeast administration. Blood lactic acid returned to normal following the administration of thiamin alone.—Charles A. Flood.

HUBENY, M. J. AND DELANO, P. J.

*Gastro-duodeno-colic Fistula; Carcinoma of the Transverse Colon. Am. J. Roent. and Radium Therap., 43:198-200, Feb., 1940.*

Hubeny and Delano report a case of gastro-duodeno-colic fistula in a female aged 45. The first clue to the diagnosis was revealed by a barium enema in which they found an irregularity of the transverse colon near the hepatic flexure, and barium in the stomach. A pathological study revealed a gastro-duodeno-colic fistula due to an adenocarcinoma. It is interesting to note that the barium meal presented no clear evidence of the condition. Hubeny and Delano stress the importance of the radiologic method of examination in the diagnosis of this condition.—Maurice Feldman, Baltimore, Md.

GERSHON-COHEN, J., SHAY, H. AND FELS, S. S.

*The Relation of Meal Temperature to Gastric Motility and Secretion. Am. J. Roent. and Therap., 43:237-242, Feb., 1940.*

Gastric temperatures were made in 24 subjects. These were obtained with a series of three iron-constantan thermocouples passed into the stomach with the leads conducted to the potentiometer through one side of a partitioned or double-barrelled Miller-Abbott tube. The normal gastric temperature ranged from 97.4 to 99.6 degrees. They found that cold meals begin to leave the stomach almost immediately, with a rapid transit through the jejunum and ileum. As the gastric temperature returns to normal the evacuation slows down. The hot meal however, shows an immediate retardation of evacuation, but soon empties normally.

Gastric secretory changes were observed with the cold meal; the secretion were temporarily depressed. The hot meal showed no appreciable abnormal deviation in secretions. They point out that summer diarrheas might be

due, partly to ice-cold drinks which produce rapid gastric evacuation.—Maurice Feldman, Baltimore, Md.

AUGHEY, ELIZABETH AND DANIEL, ESTHER PETERSON.

*Effect of Cooking Upon the Thiamin Content of Foods. J. of Nutrition, 19:285, 1940.*

Thiamin losses due to different cooking procedures were determined by the rat-growth method for a representative variety of foods. Experiments were set up to show the percentage of the thiamin originally present in the raw food that was (1) retained by the cooked product, (2) dissolved in the cooking water, and (3) destroyed.

Thiamin destruction amounted to as much as 22% in some vegetables boiled in water and additional amounts up to 15% dissolved in the cooking water. In cases where the cooking water is discarded total thiamin losses in vegetables may amount to approximately 20 to 35%. The addition of a small amount of sodium bicarbonate markedly increased the destruction of thiamin in green peas and snap beans but had no significant effect upon the thiamin content of boiled navy beans. Roasting caused a loss of 43% of the thiamin in pork loin, nearly three times as much destruction as braising. Double boiler cooking of whole grain cereals did not destroy thiamin; baking bread caused about 15% loss of this vitamin. The relative values of the different cooked foods in meeting the daily human requirements for thiamin are discussed.—A. E. Meyer.

REHM, PEGGY AND WINTERS, JET C.

*The Effect of Ferric Chloride on the Utilization of Calcium and Phosphorus in the Animal Body. J. of Nutrition, 19:213, 1940.*

A comparison of the amounts of total ash, calcium, and phosphorus in the bodies of animals on an unsupplemented diet with the amounts in bodies of animals on a diet supplemented with enough ferric chloride to combine with one-half the phosphorus of the diet was made, and it was shown that the addition of ferric chloride resulted in a considerable reduction in the amounts of total ash, calcium and phosphorus at the end of 30 days.

Results of this experiment indicate that ferric chloride has a detrimental effect on calcium and phosphorus metabolism.—A. E. Meyer.

STEWART, HAROLD L.

*Induction of Gastric Tumors in Strain A Mice by Methylcholanthrene. Arch. Path., 29, p. 153, Feb., 1940.*

The author reviews briefly the literature on the experimental production of tumors in animals. He then details experiments on 30 strain A male mice into the stomach wall of each of which he injected 0.03 cc. to 0.05 cc. of a solution containing 10 mg. of methylcholanthrene in liquid petrolatum. As the stomach of the mouse is divided sharply into two chambers, the cardiac portion which is lined with squamous epithelium and the pyloric portion lined with glandular epithelium, he made his injections into the anterior wall of either one or both of these two chambers. After survival periods of from 6 to 17 months the animals were examined postmortem and studied.

In 4 animals squamous cell carcinoma of the stomach developed, and in 4 squamous papilloma. In addition to the tumors there was noted in different animals at autopsy hyperplasia of the gastric mucous membrane, adenomatous tumors of the lungs, and other, chiefly inflammatory, lesions in various organs. No tumors developed in 13 control mice in which yarn or thread soaked in liquid petrolatum had been stitched into the wall of the stomach.—N. W. Jones, Portland, Oregon.

MILLER, H. G.

*Myasthenia Gravis and the Thymus Gland. Arch. Path., 29, p. 212, Feb., 1940.*

The association of a tumor of the thymus with myasthenia gravis was first described by Weigert in 1901. The

author reviews the literature on the subject and reports the autopsy findings in 5 further cases. In 2 cases an encapsulated tumor of the thymus was found associated with remnants of normal thymus; in 2 a persistent thymus was observed, with marked peripheral epithelial hyperplasia in 1 case; and in 1 case the thymus was not identified. The total number of reported cases of myasthenia gravis in which adequate autopsy was done is now 87, in which 41 revealed distinct anatomic lesions of the thymus gland. E. T. Bell stressed, in his study, the specific character of the changes in the thymus—a reversion to a fetal type of structure produced by the disproportionate hyperplasia of the epithelial elements, which are relatively inconspicuous in the adult gland—and pointed out that such an appearance is found almost exclusively in tumors associated with myasthenia gravis.

It is suggested that all patients with myasthenia gravis be carefully studied roentgenologically for thymic involvement, and that irradiation and surgical removal, in appropriate cases, be employed in the treatment of this disease.—N. W. Jones, Portland, Oregon.

WEINHOUSE, SIDNEY AND HIRSCH, EDWIN F.

*Chemistry of Atherosclerosis. Arch. Path., 29, p. 31, Jan., 1940.*

The authors report studies to determine further, if possible, the cause and importance of the lipid deposits in the lining of the aorta and larger arteries. They refer briefly to work already done and state succinctly the two opposing views now held as regards the significance of these deposits: the one that lipid deposit is incidental and dependent upon primary focal lesions in the media, the other that the essential factor is the penetration of plasma lipids into the intima.

The authors have attempted to determine the variations of the lipid constituents and of the calcium content of the intima and of the media of the aorta with increasing age and with increasing severity of the atherosclerotic process. Their material for chemical analysis consisted of aortas obtained during routine necropsies at St. Luke's Hospital. The adventitia and fat were stripped off and then the intima and the media separated one from the other. In all they analyzed 25 specimens, and they came to the following conclusions:

The lipid and calcium contents of the media of the human aorta increase with age. This is not correlated with the degree of atherosclerosis of the intima. Intima without lesions has a larger amount of lipid and a smaller amount of calcium than the corresponding media. With increasing severity of the atherosclerotic lesions of the intima and proportions of free and combined cholesterol increase until the onset of necrosis; then the combined cholesterol decreases. The proportions of the individual lipid constituents in the intima and in the simple fatty deposits of the intima correspond closely with those reported for these substances in blood plasma. These relations imply that the lipid deposits in the intima are the result of non-selective infiltration and precipitation of lipids from the plasma of the blood.—N. W. Jones, Portland, Oregon.

SHAFFER, JAMES MILO.

*Disease of the Liver in Hyperthyroidism. Arch. Path., 29, p. 20, Jan., 1940.*

The author reports on the histological changes in the liver in 24 cases of hyperthyroidism which came to autopsy at the Cincinnati General Hospital during the period from 1926 to 1938. These changes were sufficiently marked when compared with the findings in 100 selected control cases to justify the conclusion that a relationship between thyrotoxicosis and liver damage exists. There was loss of liver weight, fatty infiltration, cirrhosis and lymphocytic infiltration in the periportal regions in greater frequency and severity in these 24 cases than in the group of control cases. The average weight of the liver in the thyrotoxic group was 1275 gm., in the control group 1582 gm.

Fatty infiltration occurred in 92 per cent as against 56 per cent; inflammatory changes in 83 per cent as against 24 per cent. Cirrhosis occurred in 25 per cent and in 4.7 per cent in 1431 consecutive routine necropsies.

The author concludes, despite the limited number of cases studied, that the character of the changes in the liver in fatal cases of thyrotoxicosis appears sufficient to explain the clinical evidences of hepatic insufficiency.—N. W. Jones, Portland, Oregon.

VON GLAHN, WILLIAM C. AND FLINN, FREDERICK B.

*The Effect of Yeast on the Incidence of Cirrhosis Produced by Lead Arsenate. Am. J. Path., XV, 6:771, Nov., 1939.*

In a previous publication (Arch. Path., 25:4-488) the authors recorded the experimental production of cirrhosis of the liver in rabbits by copper arsenate, lead arsenate and sodium arsenate; and also the fact that the incidence of the cirrhosis could be reduced by certain diets—notably carrots and cabbage.

In another series of rabbits fed a standard diet of alfalfa and oats, to which lead arsenate was given because of its marked cirrhogenic effect and its wide use commercially as sprays and dusting powders on growing fruits and vegetables, 3 gm. of powdered brewer's yeast was given to each rabbit. The control animals thrived on the diet plus the yeast and were sacrificed at the end of 384 days. In the group of 13 rabbits given small daily doses of the arsenate 46 per cent had cirrhotic changes in the liver. In another series of 7 rabbits given the same daily doses of the arsenate, but without the addition of yeast to the diet, cirrhosis was present in 85 per cent.

There was found no apparent relation between the amount of hepatic glycogen and the quantity of arsenic in the liver, nor was there seen any connection between the glycogen content and the incidence of cirrhosis.—N. W. Jones, Portland, Oregon.

WEITZEN, MAX.

*Chronic Gastritis Caused by Gastric Bezoar. New York State J. of Med., Jan. 15, 1940.*

A 22 year old married woman first complained of sudden severe epigastric pain following a dish of shrimps, which was relieved by treatment in a few hours. During the year following there were several other similar attacks after eating other foods, which attacks were relieved rather quickly. For one month previously she had daily epigastric distress, 2 to 3 hours after meals, associated with nausea, vomiting occasionally, belching and flatulence. In addition she complained of the sensation of heat, dyspnoea, fatigue and frequency of micturition. There was a constant craving for all kinds of food and drink, which was only relieved by continuous eating and drinking. In spite of this she lost 10 lbs. during this month. Stomach X-rays revealed irregular swollen rugae, the picture of gastritis verrucosa or pseudo-polyposis. A gastric analysis yielded extraneous material, which on microscopic examination proved to be a mixture of human hair fibres, with cotton and wool threads. The patient worked as a label sewer on white-goods garments, and was in the habit of biting off the loose ends of the threads. Gastric lavage resulted in complete recovery.—Philip Levitsky, Montreal, Can.

CROHN, B. B. AND YANUS, H.

*Primary Ileocecal Tuberculosis. New York State J. of Med., Feb. 1, 1940.*

The authors feel that true primary ileocecal tuberculosis is a much rarer disease than most people believe. They reviewed 4,800 autopsies and all the surgical specimens at Mt. Sinai Hospital for the period 1926 to 1938. The necropsy material yielded only 1 case of primary intestinal tuberculosis. Seven other cases were discovered among the surgical specimens. The cases were evenly divided as to sex. Seven occurred in the second and third decades,



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the eighth was in a woman of 55. Four were white natives, 2 Puerto Ricans, 1 Hindu and 1 Negro. Pathologically the lesions varied from simple multiple discrete ulcerations to ulcerations with granulomatous reaction and localized mass formation. Mesenteric lymph nodes were enlarged, but did not caseate as a rule. In 1 case a caseated lymph node had broken into the thoracic duct with resulting generalized miliary tuberculosis. Most prominent symptoms were moderate diarrhea, low grade fever, and colicky abdominal pains during defecation. Loss of weight was marked as was secondary anemia. Sooner or later a mass appeared in the R.L.Q. Radiologically the picture is easily confused with terminal ileitis. An irritable non-filling cecum is common to both. Strictured areas are more characteristic of tuberculosis but the typical "string sign" is rarely seen. The prognosis is not good even after resection. Of the authors' 8 cases, 1 was not improved, 2 had recurrences, 2 died, and 1 improved, and 1 apparently cured. All cases showed histological lesions typical of tuberculosis. In only 2 cases could acid-fast organisms be demonstrated. Guinea-pig inoculation, attempted in 2 cases, failed to reproduce the disease in 1 instance.—Philip Levitsky, Montreal, Can.

BINKLEY, GEORGE E.

#### *Treatment of Operable Rectal Cancer.*

Early recognition is very essential to successful treatment of this disease. A thorough rectal and sigmoidoscopic examination must not be withheld from any patient presenting himself with rectal symptoms, however, insignificant. No radical measures should be adopted until the diagnosis has been definitely established by means of biopsy. The most commonly accepted operation, today, is the abdomino-perineal resection. The author discusses the variations of the well recognized surgical procedures in use today. Careful pre- and post-operative management will contribute substantially to a lowered mortality. Of 61 patients operated on 47.5% survived 5 years. Radiation therapy has been used alone or in conjunction with radical surgery. Radiation alone is most suitable in the early cases, for cancers measuring 4 cms. in diameter, or less. In this group the results are superior to those of surgery alone. In 31 patients with lesions of 4 cms. or less, where irradiation by itself was used, 24 are alive and clinically well. Fifteen have been observed for 3 years post radiation, and 9 have survived 5 to 10 years. Combined radiation and surgery is applicable in advanced, but still operable cases.—Philip Levitsky, Montreal, Can.

BARBER, ROBERT F.

#### *Acute Abdominal Condition.*

The major exciting factors involving the abdominal organs from the point of view of etiology are trauma, infection and obstruction, and the effects which follow will depend as to whether the solid or hollow organs are affected. Trauma may be an external blow damaging the intra-abdominal viscera without breaking the skin, or a penetrating wound. Infection may be acute or chronic, specific or non-specific, circumscribed or diffuse. Obstructions give rise to diverse clinical syndromes. Two conditions must always be excluded in any acute abdomen, namely angina pectoris and diabetic acidosis. The only constant symptom common to all abdominal conditions is pain. Pain must be analyzed as to type of onset, site, radiation, character, intensity, rhythm and duration. The location of tenderness is extremely important. The most tender quadrant of the abdomen will contain the inflammatory process. Nausea and vomiting are nearly always present, but are of no diagnostic importance. Flat X-ray films often give information as to the presence of distention, fluid, free gas, calcium containing shadows, and enlargement of the solid organs. In the management of abdominal cases, the use of 4 procedures is recommended. In distention of the g-i tract, decompression of the stomach can be achieved by the Levin tube according to the method

of Wangenstein, the Miller-Abbott tube for the small intestine and the rectal tube for the large bowel. The inhalation of oxygen sometimes accomplishes the same result.—Philip Levitsky, Montreal, Can.

HOLLAND, A. L. AND LOGAN, V. W.

#### *Cancer Developing in a Herniated Portion of the Stomach.*

A male 76 years old complained of dysphagia, substernal and epigastric distress and loss of 12 pounds of weight in 2 months. Esophagoscopy and X-ray studies revealed an extensive ulcerating carcinoma in a herniated stomach. The patient received one course of X-ray therapy. He died 2½ years after onset of symptoms.—Philip Levitsky, Montreal, Can.

MORTON, JOHN J.

#### *Acute Pancreatitis. New York State J. of Med., Feb. 15, 1940.*

Among the contributing etiological factors are trauma, regional infections. Toxic factors consist of alcoholism and drugs, obstruction to the biliary passages. There is also circulatory stasis, general or local as thrombosis or embolism of the pancreatic vessels. For therapeutic purposes the author divides his cases into 3 categories—acute edematous pancreatitis, acute hemorrhagic or necrotic and pancreatic abscess. A list of symptoms is included. Pain is present in 100% of all types. It is usually steady, persistent, requiring large doses of morphia, often without relief. The pain usually starts in the epigastrium, and may radiate to either costal margin, the back, either shoulder or axilla. Vomiting is seen in 75%, jaundice in 1/3 of cases, and constipation is usually present. Cyanosis is only seen in a few. The degree of shock depends upon how soon the patient is seen by the physician. The temperature is usually normal or subnormal; the pulse 100 to 110; average white blood count around 17,000. The outstanding physical sign is tenderness, most frequently in the epigastrium, though it may vary somewhat in position. Spasm is seen in 50%, distention in 38%. High blood sugars are recorded in a few cases. The condition is often missed. It requires differentiation from gastric and duodenal perforation, intestinal obstruction, mesenteric thrombosis, coronary occlusion. In 1 case abdominal paracentesis yielded the characteristic prune juice fluid. If diagnosis is made or suspected, most surgeons prefer immediate operation. The author's results are: acute edematous pancreatitis, 22 cases, 9 deaths, mortality 40.9%; acute hemorrhagic or necrotic, 13 cases, 8 deaths, mortality 61.5%; pancreatic abscess, 7 cases, 2 deaths, mortality 40%.—Philip Levitsky, Montreal, Can.

RAWLS, WM. B.

#### *Carcinoma of the Colon in a Girl of 13. New York State J. of Med., Feb. 15.*

Complaints were pain and soreness over the entire abdomen for 7 months, anorexia, weakness and loss of weight. Distention and tenderness were noted over the entire abdomen, most marked in the left upper quadrant. A mass, the size of an orange was felt in the left hypochondrium. Two stool examinations were negative for occult blood. X-ray showed a constriction of the transverse colon just proximal to the splenic flexure with calcification around it. Biopsy revealed a gelatinous carcinoma of intestinal origin. Patient died in about 1 year following onset of symptoms.—Philip Levitsky, Montreal, Can.

SCHOENLEBER, A. W.

#### *Food Handler as Transmitter of Amebiasis. Am. J. of Tropical Med., Jan., 1940.*

The author takes issue with Sapero and Johnson, who reported in American Journal of Tropical Medicine, 19: 255, 1939, that transmission of amebiasis by infected food handlers was uncommon. He reports his results of a



survey of a group of 1500 Americans living in an industrial colony on the island of Aruba, which is located just off the northern coast of Venezuela. The majority of the population of this group were mid-western and eastern Americans who traveled directly to Aruba, with no intermediate stops. Their lives were secluded from the outside villages since all recreational and essential facilities were provided by the company in this modern settlement. Drinking water was brought by tanker from Bayonne, N. J., which was chlorinated on arrival, and tested for B. Coli. All food stuffs were brought from U. S. A. Bread was baked in the company bakery. One-third of the group ate in the company mess, where the food handlers were natives or Chinese, who lived in the tropics for many years. There were modern sanitary facilities, as sewage disposal, discharged into the sea, and there were practically no flies. The group had no opportunity to contact amebic infection from outside the camp, and within the camp, the only source of infection possible was the carrier. Of the native population 33.1 3% were infected. The Americans gave a rate of 25.57%. During the first year of the survey the frequency rate for amebic colitis was 36.84 per 1000 per annum.

This study indicates that infection through food handlers plays a most important part, since it was responsible for a 25% rate of infection, compared with a rate of not more than 10% in the American districts from which these Americans originated. Treatment of all the food handlers was instituted as well as proper instruction in sanitary cleansing of hands and finger-nails. After 3 years, the rate for infection dropped to 1.92%, with a colitis frequency of 0.61 per 1000. — Philip Levitsky, Montreal. Can.

EISELE, C. WESLEY.

*Changes in the Acid-base Balance During Alkali Treatment for Peptic Ulcer. A Clinical Analysis of Alkalosis in Twenty-eight Patients. Arch. Internal Med., 63(6):1048-1067, 1939.*

Under the Sippy management for peptic ulcer subjects usually develop a tolerance to alkalis. While all patients under this form of therapy develop some degree of chemically apparent alkalosis, clinical alkalosis develops in only a few and symptoms of this condition are not correlated with the degree of chemical alkalosis present. The work of the kidney during the course of alkali treatment is greatly increased, the urinary excretion of solids being nearly doubled. In these patients exhibiting chemical alkalosis while under treatment for peptic ulcer a high incidence of preexisting renal damage was found — W. C. Hunter (Courtesy of Biol. Abst.).

TOWNSEND, S. R. AND MILLER, E. S.

*The Use of Vitamin K and Bile Salts in the Prevention and Control of the Hemorrhagic Diathesis in Obstructive Jaundice. Canadian Med. Assn. J., 41:111-114, 1939.*

10 cases of obstructive jaundice with lengthened bleeding and clotting times were given 1800 to 10000 units of Vitamin K and 1 to 3 g. of bile salts daily and the clotting time returned to normal in 5 to 12 days in 9 of the cases. — E. M. Boyd (Courtesy of Biol. Abst.).

BARGEN, J. ARNOLD, JACKMAN, RAYMOND J. AND KERR, JACK G.

*Studies on the Life Histories of Patients with Chronic Ulcerative Colitis (Thrombo-ulcerative Colitis), with Some Suggestions for Treatment. Ann. Int. Med., 12(3):339-352, 1938.*

871 cases of thrombo-ulcerative colitis which had been followed from 7 to 14 years after first observation are described. Predisposing factors and factors affecting relapses are given and the types, major complications, and sequelae of the disease described. The progress of the invasion from the rectum toward the cecum is indicative of

the destructive nature of the disease and this may mean surgical intervention though such patients are poor surgical risks. The authors recommend a well-ordered regimen to be followed without deviation by these patients for months and years. — M. L. Ilsley (Courtesy of Biol. Abst.).

EHRENFELD, IRVING, BROWN, AARON AND STURTEVANT, MILLS.

*Studies in Gastro-Intestinal Allergy. Allergy in the Pathogenesis of Peptic Ulcer. J. Allergy, 10(4):342-348, 1939.*

Of 72 allergic patients 4 had peptic ulcer. Of 75 patients with proved peptic ulcer, 8 had one or more allergic manifestations. These figures were no greater than the incidence of peptic ulcer in the general population. — J. H. Black (Courtesy of Biol. Abst.).

EUSTERMAN, GEORGE B.

*Common Gastro-Intestinal Emergencies and Their Medical Aspects. Ann. Int. Med., 12(3):306-316, 1938.*

A wide variety of diseases and disorders frequently gives rise to disturbance principally gastro-intestinal in nature and of sufficient severity to constitute an emergency, e.g., perforation, hemorrhage and obstruction. The pulmonary, vascular, andcretory systems frequently show symptoms of gastro-intestinal nature and therefore overshadow the less spectacular but more diagnostic symptoms that show the organ that is at fault, e.g., pneumonia, angina pectoris, acute coronary occlusion, and pelvic disease. Toxemia (extrarenal uremia, hypochloremia, azotemia, alkalosis, nondiabetic acidosis) is a frequent occurrence and constitutes an emergency incident to certain forms of treatment, preoperative states or postoperative complications. Hypoproteinemia is of less frequency and gravity but is an important cause of edema and postoperative impairment of gastric motor function. — M. L. Ilsley (Courtesy of Biol. Abst.).

FIESSINGER, H., BENARD, H., HERBAIN, M., DERMER, L. ET BAREILLIER, G.

*Nouvelles Recherches sur les Modifications de la Glycémie au Cours de la Perfusion du Foie. Ann. Med., [Paris] 45(1):5-36, 1939.*

By exercise of certain precautions, perfusion of the liver by homologous, defibrinated, citrated and reoxygenated blood will bring about stability of hepatic glycogen and likewise a certain amount of glycemia in the perfusate. Addition of preps. containing insulin induces a considerable increase of the glycemia. The hypoglycemic action of insulin upon an animal is not parallel to its change of glycogen in the liver during perfusion. Adrenalin even in small dosages increases glycemia greatly and its effect is more lasting than that of insulin. This effect is not due to vasoconstrictive action. Other hormones such as thyroxine, extract of the pituitary and folliculine have no influence upon hepatic glycogen. The effects noted above are not exercised upon glycogen directly; they act upon the glycogenase. — T. D. Beckwith (Courtesy of Biol. Abst.).

GIBSON, WILLIAM R. AND ROBERTSON, H. E.

*So-called Biliary Cirrhosis. Arch. Path., 28(1):37-48, 1 fig., 1939.*

Hepatic cirrhosis may be defined as including parenchymal degeneration, fibrosis and nodular parenchymal regeneration. From a series of 244 cases of biliary obstruction and obstructive jaundice, 21 cases, or 8.6 per cent were separated out in which these conditions were associated with hepatic cirrhosis as defined. In 10 of these 21 cases the biliary obstruction was due to postoperative stricture of the common duct, in 6 cases to choledocholithiasis, in 2 cases to carcinoma of the ampulla of Vater and in 3 cases to other malignant lesions. An intermittent

type of obstructive jaundice was present in 15 of these 21 cases, or 71.4 per cent. The average case duration from the first onset of jaundice to death was 3 years. These factors may be involved in the production of regeneration of these cases. It is suggested that the term "biliary cirrhosis" be dropped and the designation "cirrhosis from biliary obstruction" be employed for the infrequent combination of biliary obstruction, obstructive jaundice and true hepatic cirrhosis. Cases in which hepatic parenchymal damage without signs of regeneration follows obstruction of the bile ducts should be classified as instances of hepatic atrophy.—Authors (Courtesy of Biol. Abst.).

FLOREY, H. W., JENNINGS, M. A., JENNINGS, D. A. AND O'CONNOR, R. CASTRO.

*The Reactions of the Intestine of the Pig to Gastric Juice.* *J. Path. and Bact.*, 49(1):105-123, 3 pl., 1939.  
Various technical procedures are described for comparing the resistance of the duodenum to gastric juice with that of the jejunum and ileum. The duodenum has a much greater resistance than other parts of the intestine. These findings are consistent with the view that Brunner's glands are concerned in a protective mechanism against gastric juice. Histological and endoscopic observations on parts of the intestine exposed to gastric juice are described.—Auth. summ. (Courtesy of Biol. Abst.).

GOFFIN, RENÉ.

*A Propos des Effets de l'hyperglycémie sur la Sécrétion Biliaire.* *Compt. Rend. Soc. Biol.*, 130(12):1343-1344, 1939.

Hyperglycemia in dogs was induced by 800 mg./kg. of glucose (intravenously), previously pancreatectomized and by using animals with choledochus fistula where hyperglycemia in the receptor was progressively increased by blood transfusion of a pancreatectomized donor. The 2 groups simultaneously received 30 mg./kg. of excretine (intra-saphenally) in order to produce biliary hypersecretion. While hypoglycemia inhibits biliary response to excretine injection, hyperglycemia brings about hepatic secretion which is markedly higher than under normal conditions.—H. Simons (Courtesy of Biol. Abst.).

HALL, E. M. AND MORGAN, W. A.

*Progressive Alcoholic Cirrhosis. A Clinical and Pathological Study of 68 Cases.* *Arch. Path.*, 27(4):672-690, 1939.

A group of 68 active, or subacute cases of cirrhosis of the liver were selected from among 1,300 autopsies performed according to the following criteria: large liver (2000-5000 gm.), actively proliferating connective tissue, and the presence of hepatic necrosis. 50 per cent of the livers were excessively fatty, 50 per cent were jaundiced, some were edematous, many showed polynuclear, as well as round cell infiltration. About 90 per cent showed "alcoholic" hyalin in the degenerating hepatic cells. Patients with cirrhosis were found to suffer from chronic alcoholism in 80-90 per cent of cases. Since chronic alcoholism was so frequently associated with dietary deficiency and avitaminosis, cirrhosis of this type might be due to excessive use of ethyl alcohol plus dietary deficiency. In addition, susceptibility of the individual to alcohol as a drug was probably a factor of the individual since only 5 or 6 per cent of chronic alcoholics developed cirrhosis.—E. M. Hall (Courtesy of Biol. Abst.).

HOLDEN, HENRY FRANCIS AND LEMBERG, RUDOLF.

*The Ultra-violet Absorption Spectra of Bile Pigment Iron Compounds and of Some Bile Pigments.* *Australian J. Exp. Biol. and Med. Sci.*, 17(2):133-143, 9 figs., 1939.

The u.-v. absorption of various hematin compounds which are intermediate between protohematin and biliverdin, and also of some bile pigments, is studied. Of all these compounds only hydroxyporphyrin-hemochromogen,

which still contains the intact porphyrin ring, possesses a typical Soret band, similar to that of protohematin compounds and porphyrins. The bile pigment-iron compounds verdohemochromogen, choleglobin and cholehemochromogen are devoid of this band as are bile pigments. These observations confirm the open ring structure attributed by Lemberg to these hematin compounds on the basis of chemical facts.—H. F. Holden (Courtesy of Biol. Abst.).

MEERSEMAN, F.

*High Concentrations of Injectable Liver Extracts in the Treatment of Insufficiency of the Liver.* *Bull. et Mem. Soc. Med. Hop. Paris*, 55(21):951-955, 1939.

Liver extract (10 g. liver = 1 cc.) was given daily or 10-12 doses every 2 days, was given to 70 cases in 3 main categories: benign infectious icterus (20 cases); chronic dysfunction (11 cases); minor dysfunction "petits hépatiques" (36 cases). Convalescence was notably shortened, icterus regressed rapidly if treated early, complaints such as vomiting and asthenia were reduced. The injcs. were suggested preparatory to surgical intervention.—E. Huene (Courtesy of Biol. Abst.).

PENNER, ABRAHAM AND BERNHEIM, ALICE IDA.

*Acute Postoperative Enterocolitis, a Study on the Pathologic Nature of Shock.* *Arch. Path.*, 27(6):966-983, 2 figs., 1939.

In a study of a correlation between the pathologic findings and the clinical state immediately preceding death, it was found that patients showing focal ulcerations in the small and large intestines were invariably in shock. The physiologic mechanisms participating in the maintenance of the cardiovascular system in shock, are invoked to explain the occurrence of these lesions.—A. Penner (Courtesy of Biol. Abst.).

PENNER, ABRAHAM AND BERNHEIM, IDA.

*Acute Postoperative Esophageal, Gastric and Duodenal Ulcerations.* *Arch. Path.*, 28(2):129-140, 1 fig., 1939.

A report of four cases of ulcerative lesions in the esophagus, stomach and duodenum which appeared postoperatively or subsequent to diabetic acidosis, is given. A reconstruction of the sequence of histologic events on the basis of observations indicated that the earliest change consisted of a marked distension in capillaries and venules which was seen in the mucosa in the stomach, and in the submucosa in the esophagus and duodenum. An anatomical explanation for this was offered. Edema fluid accumulated and focal hemorrhages were frequently observed; these were due to the increase in permeability of the capillaries resulting from the stasis which was the consequence of the arteriolar constriction coming on in response to shock. The further progress of the process resulted in necrosis of the tissues in the foci involved. The vasomotor mechanisms which constitute the response to shock, evidently produced these lesions.—Authors (Courtesy of Biol. Abst.).

WHITE, E. G.

*The Effect of Carbon Tetrachloride on the Liver of the Pig, with Especial Reference to Experimental Cirrhosis.* *J. Path. and Bact.*, 49(1):95-103, 2 pl., 1939.

In pigs weighing 7-17 kg. and aged 25-66 days the subcut. inj. of CCl<sub>4</sub> (0.6 cc. per kg. body weight) seldom caused clinical symptoms although necrosis of the central half of each liver lobule occurred. Repair was complete in a week. With some animals, however, a dose as small as 0.2 cc. per kg. body weight caused death within 12 hours. Repeated injections at 4- to 5-day intervals led to cirrhosis, the pathogenesis of which was studied by examining liver samples removed at intervals and finally at autopsy. The most severe cirrhosis resulted from the largest dose—

36 injections of 0.2 cc. per kg. body weight. There was no ascites, icterus, nor splenomegaly.—E. G. White (Courtesy of Biol. Abst.).

CULMER, C. U., ATKINSON, A. J. AND IVY, A. C.

*Depression of Gastric Secretion by the Anterior Pituitary-like Fraction of Pregnancy Urine. Endocrinology, 24(5):631-637, 1 fig., 1939.*

A study of the effect of the parenteral adm. of the APL fraction of human pregnancy urine on the gastric secretory response to a test meal was made in 5 female dogs with Pavlov pouches. After suitable control tests, 1000-2000 R.U. of antuitrin-S and 5000 U. of follutein were given parenterally  $\frac{1}{2}$  hour before the test meal. In 4 of the 5 dogs, in 7 out of 8 tests, significant to marked decreases in volume and acid output occurred each day during a 5-day period of treatment. In 4 of 7 instances the secretory response returned to normal one day after cessation of treatment; in the other, 3, return was slower.—D. Permar (Courtesy of Biol. Abst.).

GOFFART, M. ET BACQ, Z. M.

*Teneur en Acetylcholine due Tube Digestif Apres Vagotomie et Enervation Locale. Compt. Rend. Soc. Biol., 130(12):1373-1375, 1939.*

In dogs bilateral subcardiac vagotomy (by thoracic way) or complete local denervation of all the fibers accompanying the mesenteric artery and vein of an iliac loop did not alter the acetylcholine level after operation (on the 10-13th and 6-7th day respectively). By these properties the peripheral intestinal neuron clearly differed from the ganglionic neuron whose cholinergic neuron innervated the submaxillary and parotid glands, iris and heart, where a marked fall in the acetylcholine content of the denervated organ was noticed by section of preganglionic fibers.—H. Simons (Courtesy of Biol. Abst.).

BOZLER, EMIL.

*Electrophysiological Studies on the Motility of the Gastro-Intestinal Tract. Am. J. Physiol., 127(2):301-307, 4 figs., 1939.*

The action potentials of the small intestine and stomach were recorded during pendular and segmenting movements and during peristalsis. The potentials are interpreted as impulses conducted within the syncytial musculature. Usually each contraction is accompanied by a burst of impulses like a tetanic contraction of skeletal muscle. The frequency of discharge varies from 1 per second in the stomach to 10 per second in the small intestine of the rabbit during a peristaltic rush. Gradation of contractions is possible by variations in the number and frequency of impulses and by participation of different fractions of the whole musculature of the organ.—E. Bozler (Courtesy of Biol. Abst.).

CLARK, BYRON B., SHIRES, E. B. S., JR., CAMPBELL, E. H. AND WELCH, C. STUART.

*The Action of Syntropan on the Gastro-Intestinal Tract. J. Pharmacol. and Exp. Therap., 66(4):464-478, 1939.*

On excised intestine, syntropan (the phosphoric acid salt of the tropic acid ester of 3-diethylamino-2, 2-dimethyl-1-propanol) in small doses, antagonized parasympathetic drug stimulation, but in larger doses produces greater smooth muscle depression than atropine. About 100 times more syntropan than atropine is required to produce the same degree of depression. In the unanesthetized dog, syntropan antagonizes the stimulating effect of mecholyl, morphine and pitressin. The antagonism of morphine and pitressin by syntropan is much greater than for an equivalent dose of atropine and suggests that the antagonism of smooth muscle stimulants may be obtained by syntropan in the intact animal. Syntropan produces relaxation of the tone of the stomach and inhibition of peristaltic activity. The effect of syntropan on gastric secretion excited by a

meat extract meal and histamine is weak as compared with atropine.—Authors (Courtesy of Biol. Abst.).

CRITTENDEN, PHOEBE J.

*Effects of Anesthetics on the Response of Submaxillary and Pancreatic Glands to Prostigmine and Physostigmine. Proc. Soc. Exp. Biol. and Med., 41(2):367-370, 1939.*

Dogs were anesthetized with either Na pentobarbital, chloralose, or paraldehyde. Prostigmine and physostigmine were administered intraven., in doses of 0.005 mg. to 0.2 mg. per kg. The effects on the pancreatic and submaxillary glands, heart rate and blood pressure were recorded. The smaller doses of prostigmine were more potent stimulants of pancreatic and submaxillary secretion than were similar doses of physostigmine. A reversal in the response of both glands was noted with the larger doses of prostigmine. Chloralose and paraldehyde anesthesia diminished the response of the glands to both drugs.—P. J. Crittenden (Courtesy of Biol. Abst.).

MCGEE, ANDREW J.

*Vitamin B<sub>1</sub> in Alcoholic Polyneuritis. With a Report of 48 Cases. Illinois Med. J., 75(5):470-473, 1939.*

In a group of 25 patients with alcoholic polyneuritis treated by subcut. hypodermic inj. of Vitamin B<sub>1</sub> (thiamin chloride) and a control group of 23 patients receiving only the Vitamin B<sub>1</sub> contained in the diet there was practically no difference in the time required for complete alleviation of symptoms. The severity of the symptoms and the time required for recovery seem to be directly proportional to the duration of the neuritis.—Authors concl. (Courtesy of Biol. Abst.).

WARREN, RICHARD.

*A Technic for the Study of Gastric Absorption in Man. Proc. Soc. Exp. Biol. and Med., 41(1):287-291, 1939.*

By a modified Miller-Abbott tube system a method for isolating the stomach for physiological experimentation in normal humans was developed. A double balloon blocks the pylorus, while an aspirating tube in the duodenum detects any escape of gastric material. The technic was successful in approximately 1 out of every 3 attempts.—R. Warren (Courtesy of Biol. Abst.).

ROSENBLUM, HAROLD.

*Cigarette Smoking: Its Effect on the Volume and Acidity of the Gastric Juice with Particular Reference to Duodenal Ulcer. California and West. Med., 49(3):191-194, 1938.*

The author studied the immediate effect of the smoking of a single cigarette upon the acidity of volume of the gastric juice of fasting patients with and without peptic ulcer. This resulted in a significant average increase in volume of gastric juice and in free and total acidity of 19 patients with duodenal ulcer and to a lesser extent in 23 patients without duodenal ulcer.—M. L. Ilsley (Courtesy of Biol. Abst.).

JACOBSON, W.

*The Argentaffine Cells and Pernicious Anemia. J. Path. and Bact., 49(1):1-19, 2 pl., 1939.*

The argentaffine cells in man and the pig occur in the cardia and the pylorus but are practically absent from the corpus of the stomach. They are very numerous in the upper duodenum, quite frequent in other parts of the small intestine and occur also in the colon and appendix, though to a lesser degree. The granules of the argentaffine cells of the gastro-intestinal tract contain a pterine, closely related to xanthopterin and uropterine, and a carbohydrate (probably a desoxy-pentose). There is a striking parallelism between the distr. of argentaffine cells and the localization of the principle active against pernicious

anemia in the mucosa of the gastro-intestinal tract of man and of the pig. In 12 cases of pernicious anemia and 2 cases of sprue with macrocytic anemia, the argentaflavine cells were almost completely absent. In 3 cases of macrocytic anemia which did not respond to liver treatment, and in secondary anemias the argentaflavine cells were only slightly affected. The argentaflavine cells evidently played a part in normal erythropoiesis.—W. Jacobson (Courtesy of Biol. Abst.).

MORRISON, J. L., SHAY, HARRY, RAYDIN, I. S. AND CAHOON, R.

*Absorption of Glucose from the Stomach of the Dog. Proc. Soc. Exp. Biol. and Med., 41(1):131-134, 1939.*

Varying concs. of glucose were placed in the stomach of the dog in order to determine whether glucose was absorbed. The method used permitted of qualitative studies. Glucose was absorbed from the stomach when present in hypertonic solns. When the total amount of glucose in the stomach gave evidence that absorption had taken place there was a co-incidental rise in the blood sugar during the period of absorption.—I. Ravdin (Courtesy of Biol. Abst.).

MERANZE, THEODORE, MERANZE, DAVID R. AND RATHMAN, MAURICE M.

*Review of the Value of Serum Phosphatase in Diseases of the Liver. Rev. Gastro-enterol., 6(3):254-262, 1939.*

The serum phosphatase detn. is of value in differentiating obstructive jaundice (values in adults usually above 16 units) from hepato-cellular jaundice (values below 12 units in adults but up to 20 units in children and young adults).—G. H. Chapman (Courtesy of Biol. Abst.).

LAGERLÖF, HENRIK.

*The Secretin Test of Pancreatic Function. Quart. J. Med., 8(30):115-127, 1939.*

Purified secretin is used to stimulate pancreatic secretion in man. A technique is described for collecting pancreatic juice free from gastric juice. Normal variability and pathological variations in the vol. of the juice and its content of enzymes and bicarbonate are presented. The content of diastase possesses the highest functional significance.—H. G. Swann (Courtesy of Biol. Abst.).

IKEGAKI, IWATARO.

*Die Bedeutung der Leber für die Überdosierung des A-Vitamins und des Karotins. II. Die Funktion der Leber bei der Überdosierung des A-Vitamins. Zeitschr. Vitaminforsch., 9(1/2):1-8, 2 figs., 1939.*

Vitamin A in moderate doses stimulates liver function but excessive amounts are stored in the liver and damage liver function before hypervitaminosis is established.—R. A. Cowles (Courtesy of Biol. Abst.).

BONAFF, KARL M.

*Water Absorption from the Colon and Its Relation to Motility. California and West. Med., 51(3):154-156, 1939.*

230 cases with no pathology in the upper gastro-intestinal tract were studied for water content of entire evacuated meal. 71 per cent water content was found in 40 normal lower bowel cases; the water content varied from 22 per cent in the constipated to 98 per cent in the pathological colon.—M. L. Ilsley (Courtesy of Biol. Abst.).

HARRIS, H. A.

*Absorption of Fat. British Med. J., (4103):465-466, 1939.*

A correction was made in the statement of Morton and coworkers (British Med. J., August 12, 1939, p. 345) that fishes have no lymphatic system and that fats are absorbed through the mucosal epithelium. In 1769 William Hewson, partner of John Hunter, demonstrated the lymphatic

vessels in 4 spp. of fish. In 1926 R. H. Bourne, curator of the Royal College of Surgeons, made careful anatomical studies of the lymph system of the angler fish. The author refers to Absorption from the Intestine by Verzar, London, 1936, and to his own observations (Am. J. Med. Sci., 181:453, 1931).—J. B. Paton (Courtesy of Biol. Abst.).

FOLDES, EUGENE.

*The Red Blood Cells in Obstructive Jaundice. Rev. Gastro-enterol., 6(5):438-441, 1939.*

Macrocytosis and progressive anemia are the outstanding hematologic features in obstructive jaundice. The accumulation of bile acids in the plasma, with consequent acidosis, produces swelling of erythrocytes with greater tendency to disruption, resulting in a hemolytic anemia.—G. H. Chapman (Courtesy of Biol. Abst.).

NORDSTRÖM, T.

*Experimental Investigation of the Hydrochloric Acid Secretion in Scorbatic Guinea Pigs. Acta Med. Scand., 99(5):443-448, 5 figs., 1939.*

No HCl deficiency was produced in 5 guinea pigs and only slight lowering occurred in 5 others after a diet absolutely deficient in Vitamin C for 20-25 days.—J. F. Wilkinson (Courtesy of Biol. Abst.).

GOLDBERG, S. A.

*Unusual Neoplasms of the Small Intestines. Am. J. Clin. Path., 9(4):516-528, 16 figs., 1939.*

Of the 10 cases, 7 were females and 3 were males. Of 4 carcinomata, 2 were in the 2d portion of the duodenum, 1 in the 3d portion, and 1 in the jejunum. Of 6 other neoplasms, 3 were leiomyosarcomata of the jejunum, 1 a hemangiomyoma of the jejunum, 1 a metastasizing argentaflavine tumor of the jejunum, and 1 a multiple microcystic lymphangioma of the ileum.—From auth. summ. (Courtesy of Biol. Abst.).

TANTURI, CARLOS ALBERTO, BRADLEY, WILLIAM B. Y. IVY, AUDREY C.

*Action del Atophan Sobre el Hígado. [Action of Atophan on the Liver]. Rev. Assn. Med. Argentina, 53(405/406):7-9, 1939.*

Atophan in various doses up to 500 mg. per kg. injected into the femoral or splenic vein caused an increase of 300 to 800 per cent in biliary secretion in dogs. The action was also noted in vagotomized and eviscerated dogs. This effect could not be demonstrated in rabbits.—O. I. Cutler (Courtesy of Biol. Abst.).

NICOLESKO, P., STRAT, C., HÉRESKO, D. ET UNGUREANU, D. *L'inscription de la Motricité dans les Gastropathies par la Methode Viscerographique de Danielopolu Modificée. Bull. Acad. Med. Roumanie, 5(2):154-166, 1938.*

Peristaltic rhythm is studied mechanographically. The importance of abnormal curves is discussed.—F. H. Snyder (Courtesy of Biol. Abst.).

## CONNOTATIONS

H. J. SIMS

Denver, Colorado

Thompson in 1874, White in 1883, Codge in 1894, Reynolds and Hollander in 1896 were the first of the older writers to mention diverticula of the female bladder. Durrieux in 1901 found only 9 cases in a review of 118 cases in both sexes.

Hermance, an American surgeon, conceived the idea of testicular prosthesis; he performed such an operation in 1886 but did not report it until 1894. Tuffier and Raynier exploited the idea in France. Salles in 1896 wrote a thesis on the subject.

Bidard in 1853 made the first reference to bilateral malignant tumors of the testicle. Kober in 1887 found 19

recorded cases to which he added 2 cases of his own.

Rokitansky in 1861 described the left kidney in front of the right sacroiliac articulation. Weisback in 1867, Brigidi in 1880, Graser in 1895 and Sutherland and Deington in 1898 recognized similar instances.

Kunith in 1908, Peacock in 1925 and Figi and Cutts in 1931 reported actinomycosis of the kidney in children. Kretschmer and Hibbs in 1936 reported the fourth case and reviewed the literature.

Reference is usually made to a dermoid cyst of the kidney reported by James Paget in 1853. This specimen, No. 3358-A which is in the Museum of the Royal College of Surgeons, is from a sheep and not from a man. Madelung in 1887 reported such an occurrence.

Nebri in 1717, Rouppe in 1770, Monier in 1849 described traumatic cases of aneurism of the renal artery. Dourlin in 1803, Gossett in 1829, Leudet in 1852 and Danner in 1856 described spontaneous aneurism of the renal artery. Barnard's case showed calcified and cured aneurism of the right renal artery.

It is not generally known that Mery of France not only recognized but described Cowper's glands. Cowper in 1699 described two small bulbo-urethral glands now known by his name. Wasserman in 1895 observed 3 cases of primary carcinoma of these glands. DeMair, Kicher, Paquet and Herrmann. Pietzkowski, Uhle and Archer each described cases verified by microscopic examination. Blanc, Wies and Carret reported a case; however, the specimen was not submitted to microscopic study.

Wasserman in 1895 wrote of his findings in 3 cases of carcinoma of the male urethra. Thiaudiere in 1834 is usually credited with the first case report. Reference to his article refers to an observation he made in 1831. He stated a patient presented himself because of retention of urine. On introducing a sound, an obstruction which he believed to be a tumor was met. With the aid of 2 men, the patient was held while an incision was made on the superior surface of the glans, the wound was retracted with the aid of pincers, and the tumor was removed. Seventy-one days later the patient returned with the same symptoms, and the same operative procedure was carried out. The denuded area was cauterized with silver nitrate, and a rubber tube was introduced through the urethra every other day. In conclusion he remarked, "It seems to me that I have observed a true cancer." Later in the same writing, he stated that a fibrous tumor could produce a stricture.

The first complete removal of the penis was carried out by Thiersch of Leipzig in 1875. MacCormac in 1886 described 5 cases in which he made a "button-hole" in the perineum, through which he brought the urethra. Puzey in 1884 established a stab wound in the perineum for the transplantation of the urethra.

Raciborsky describes pneumaturia in 1860 and refers to the *Curiosities of Nature* published in 1671 in which is found the following: "A leading citizen of Gotha was affected by anal colic with rumbling tension of the abdomen, pain about the navel, and what is strange, wind was passed by the penis as if through the usual and accustomed channel, sometimes with and sometimes without urine." Kelly and MacCullum reviewed the case reports up to 1893.

## CONNOTATIONS

H. J. SIMS

Denver, Colorado

Marcellus Donatus in 1586 mentioned a case in which his patient was able to pass only a small amount of spermatic fluid during coitus. In 1619 Fabricius Bartholeus stated that he had observed a patient with complete retention, a result of a calculus formed of retained spermatozoa about the vesical neck. A similar case was reported by de Belgny in 1670. Douglas in 1707 described the finding of several hard bodies resembling peas in the prostate gland. He stated: "Some of the bodies were attached to the membrane covering them by small roots." Loss in 1707 recognized a

case and believed the presence of the bodies contributed to sterility. Louis in 1747 and Morgagni in 1762 described intelligently the symptoms and complications. Home in 1811 and Amussat and Marcet in 1833 admitted the etiology was unknown. Civalle in 1838 stated that no previous investigator had explained their formation. Larret in 1834, Manzoni in 1867, Robin in 1873 and Jean in 1878, each recorded an instance of calculous obstruction of the prostatic urethra. The writings of Velpeau, d'Etiolles, Thompson and Mellisson contributed to the pathology and clinical observations of the subject. Malteste in 1867 and Menage in 1880 not only discussed the symptoms but offered some measures of relief. Legueu in 1895 said: "There are no calculi of the prostate, but only of the prostatic urethra." Guyon in 1899 and his pupils, Albarran, Legueu and Pasteau in France, and Forsell in Germany, discussed the pathology, treatment and diagnosis of this obscure condition. In spite of this information Mariani as late as 1906 stated: "The existence of true calculi of the prostate is uncertain, and even though they exist, they have no history clinically."

Delassiauve in 1820, Langlet in 1877 and Volkmann in 1877 each reported torsion of a normal testis. Nicolandoni in 1885 described a similar case. Scudder in 1901 compiled 35 cases from the literature. Taylor in 1897, Le Bac and Fourier in 1921, and Peltazzi in 1924 each described torsion of the testes in a newborn.

Arnott, Gowers, Lecompte, Godard and Spry were among the older writers to associate the tendency of retained testicles' becoming malignant. It is believed Godard observed such cases before Johnson made his report in 1859. The tumor mass developed following an injury and at autopsy the tumor weighed 14 pounds. Martin in 1861 reported the first operative interference. The patient was 30 years of age and presented a double abdominal cryptorchid. In certain species of monkeys the testicles during their first week of life ascend into the abdominal cavity. They remain intra-abdominal until the 5th or 6th year of life and then descend into the scrotum. Many hibernating animals draw their testicles into the abdomen during the winter months. Inguinal hernia and cryptorchid are not uncommon among swine. In cattle, buffalo, deer and antelope, descent of the testicle occurs early in life. The descent of the testes in a horse is often not complete until several months after birth.

Furbringer in 1886 observed that spermatozoa expressed at defecation were immotile, while ejaculated semen contained normally motile cells. He concluded that secretions of the prostate gland were awakening the dormant life of the spermatozoa. This was confirmed Furbringer's observation from study in rabbits, guinea pigs and rats.

The recognition of acute dilatation of the stomach dates back to 1842, for at this time Rokitansky described a type of acute dilatation of the stomach due to compression of the duodenum by the root of the mesentery. Bamberger in 1855 called attention to the fact that infectious diseases could produce acute gastric dilatation. Brinton in 1859 endeavored to explain its pathology. In 1868 Erdmann reported a case which followed trauma. The first accurate description was given by Fagge in 1872.

Auretius described a condition "cynanche" which is believed to have been Ludwig's angina. Paulus Aegineta spoke of a similar condition which he called "paracynanche." Fothergill (1739-1746) gave an account of "Putrid Sore Throat." Ludwig gave the first accurate description of the condition which he termed "gangrenous induration of neck." Nelaton was instrumental in forcing the medical profession not to accept the disease as an entity. Delmore, a teacher of Ludwig, eventually convinced the profession that Ludwig's angina was primarily a sublingual phlegmon.

Bardeleben in 1841 showed that the spleen might be removed in healthy animals and be followed by no serious loss to the animal economy.

J. E. D. D.  
JULY, 1940

HAGGARD, HOWARD W. AND GREENBERG, LEON A.: *Studies on the Absorption, Distribution and Elimination of Alcohol. V. The Influence of Glycocol Upon the Absorption of Alcohol.* *J. of Pharm. and Exp. Therap.*, 68:482, 1940.

When glycocol is given with a small amount of alcohol the concentration in the blood not only rises more slowly but falls again sooner than when the alcohol is given without glycocol. It is shown here that in reality alcohol is not altered, combined, or destroyed by any action of glycocol. The alteration in the curves for the concentration of alcohol in the blood when administered with glycocol can be explained as due to a prolonged retention of alcohol in the stomach induced by glycocol and a correspondingly retarded absorption. When alcohol is absorbed slowly from the alimentary tract it may be oxidized as rapidly as it is absorbed and the concentration in the blood is thus kept down to an extremely low value although alcohol is still being absorbed.—A. E. Meyer.

WELCH, C. STUART AND YUNICH, ALBERT M.: *The Problem for Surgery in the Treatment of Massive Hemorrhage of Ulcer Origin.* *S. G. O.*, 70:3-662, March, 1940.

This study reviews the various procedures for treatment of active bleeding from ulcers, including the starvation and feeding methods, massive transfusion and aluminum hydroxide solutions introduced in the stomach by gastric intubation. Since none of these methods is uniformly satisfactory, attention is given to surgical treatment with the belief that mortality rates will be reduced by it.

One hundred and twenty-eight cases of bleeding peptic ulcers at the Albany Hospital are reviewed. The mortality rate was 10.2 per cent. Operations were performed on 3 patients to control hemorrhage, and standard medical routine of starvation was practiced on the remaining patients until hemorrhage ceased. Dehydration was combated by intravenous and subcutaneous transfusions of saline. Modifications of the Sippy dietary regime were followed when the hemorrhage ceased.

Age plays a part in determining the procedure to be used. Surgery is contraindicated in young people with severe bleeding, and the prognosis for people under 50 treated by medical methods is good. The patient's chance for survival is much more limited when treated surgically. When the patient is over 50, surgery is the treatment recommended though some patients are in such poor physical condition when they enter the hospital that they cannot be operated on. Adequate operation is a long and tedious procedure. The ulcer must usually be resected to control the bleeding and sometimes another operation must be performed to restore gastro-intestinal continuity.

The field for improvement in mortality rates in massive hemorrhage of ulcer origin is in the group of patients over 50, and the benefits of surgical intervention will best be seen in this group, though patients in this group are poor surgical risks.—Francis D. Murphy.

CUTLER, E. C. AND ZOLLINGER, ROBERT: *Special Monograph: Surgery of the Gall Bladder and Extrahepatic Bile Ducts.* *Am. J. Surg.*, 47:181-260, Jan., 1940.

This is an excellent review in simple language of the pre-operative, operative and post-operative procedures carried out for patients with biliary tract disease in the Peter Bent Brigham Hospital in recent years. Consideration of the diagnosis of such diseases is necessarily limited but it is of interest to note that the authors advocate submitting every patient to intravenous cholecystography before cholecystectomy unless calculi are positively shown by the oral method. In their opinion a poorly functioning gall bladder or failure of the gall bladder to be visualized by the oral test is not sufficient evidence to warrant cholecystectomy unless clinical symptoms are

overwhelmingly in favor of disease of the biliary system. Consequently ninety-four per cent of the patients subjected to cholecystectomy by them proved to have a calculus at the time of operation. The authors state that if vomiting is spontaneous and pronounced when associated with gall stones they believe that a calculus is located within the cystic or common ducts—without duct obstruction there may be nausea and induced vomiting but not involuntary vomiting—with their opinions all observers will not agree.

Upon discharge from the hospital the patient who has had cholecystectomy is instructed to follow a low fat diet and to avoid for several months those foods that proved upsetting before operation.

Cutter and Zollinger report the incidence of common duct stones recovered to be 18.5 per cent of all cases operated upon for cholelithiasis.

The authors divided cases of acute cholecystitis into three clinical groups, the first (40%) of which responds promptly to expectant treatment, the second (50%) responds more slowly and the third (5-10%) which does not respond to conservative therapy. In the treatment of patients with acute cholecystitis the writers advocate allowance of sufficient time to correct fluid balance as patients so treated are in better condition for surgery. It is the response to the general therapy which dictates the period of delay before surgery. For 123 cases of acute cholecystitis during a five year period the mortality was 7%. The average number of pre-operative days of hospitalization was five although approximately 40 per cent of the cases were operated on within forty-eight hours.—Dwight L. Wilbur.

BOWEN, ARTHUR: *Post-operative Wound Disruption and Evisceration.* *Am. J. Surg.*, 47:3-19, Jan., 1940.

Bowen has reviewed a total of 1,526 cases of wound disruption and evisceration in the literature and included a study of 24 cases occurring in the Cedars of Lebanon Hospital in Los Angeles. His studies indicate that certain primary diseases such as cancer and operations on the stomach and biliary tract predispose to evisceration. A pre-operative condition which was poor and a post-operative course complicated by distention, vomiting and cough commonly were present. The mortality in eviscerated cases was from 16-75 per cent and intestinal obstruction a serious complication.—Dwight L. Wilbur.

MCMANARA, W. L., SMITH, H. D. AND BOSWELL, C. S.: *Retroperitoneal Fibrosarcoma.* *Am. J. Cancer*, 38:63-72, Jan., 1940.

Report of 8 cases of retroperitoneal fibrosarcoma which were encountered in 2500 routine autopsies. The authors point out important clinical features of these tumors namely that they are symptomless until they have reached inoperable proportions and caused damage to vital structures, they are unaccompanied by the degree of systemic toxicity or cachexia usually associated with malignant tumors of corresponding size. The tendency to metastasis is small and the tumors are radio resistant.—Dwight L. Wilbur.

TURNER, G. GREY: *Some Notes on Abdominal Injuries.* *Brit. Med. J.*, 1:679, No. 4138, April 27, 1940.

Turner emphasizes the repair of the injured intestine by suture rather than by resection as the first line of defence. He points out that there are two things which must be avoided in suturing; one is the formation of a stricture, the other the construction of a diverticulum. The stricture can be avoided by suturing longitudinal and oblique wounds in a direction transverse to the axis of the gut; that of the diverticulum, by starting the suture at the extremities and working toward the center.

The author does not advocate the resection of the wound, nor does he trim away any of the redundant mucosa as a routine. He furthermore cautions against the use of short-circuiting operations as a hasty emergency. Enterostomy should be studiously avoided unless the patient is under continuous care. In abdominal injuries one can scarcely imagine any condition in which it would be a primary indication. After the peritoneum is opened, there is no need to get rid of all of the blood, but masses of clot should be removed. In damage to solid viscera the main indication is to arrest bleeding, either by packing or by suturing as the case indicates. In locating the injury he points out the necessity of carefully examining all the viscera, and the colon from the sigmoid to the cecum. The wounded intestine is usually more bulky and quiescent than other parts. Gunshot wounds are usually multiple. When confronted with a severe emergency the author stresses the superiority of the middle line approach. The source of hemorrhage is looked for and a search for injuries to the hollow viscus is made.—Maurice Feldman.

DAVIS, HERBERT H. AND McLAUGHLIN, CHARLES W., JR.: *Results of Treatment in Acute Appendicitis*. S. G. O., 70:3-713, March, 1940.

This study includes 963 cases of acute appendicitis, 179 of which were ruptured. In 784 cases of non-ruptured appendicitis operated on immediately, the mortality rate was only 0.5 per cent. Consequently, the authors advise immediate appendectomy for patients with a non-ruptured acute appendicitis.

In 93 cases of local spreading peritonitis, usually seen on the second day after the attack, 5 patients died, 3 from spreading peritonitis, 1 from secondary hemorrhage and one from a pulmonary embolus. Recommended treatment is immediate appendectomy with drainage, the peritonitis usually disappearing shortly.

The most serious cases were in the diffuse peritonitis group, usually seen from the third to fifth day. Treatment is questionable, some surgeons believing in immediate operation and others not operating until the symptoms clear up entirely. In 17 cases operated on immediately, the death rate was 60 per cent, while in 14 cases of delayed operation, only 14 per cent died. The 10 deaths after immediate operation were due to peritonitis. In delayed operation, which is recommended as a means of lowering the mortality rate, the preoperative management of the patient is important. The gastro-intestinal tract is given absolute rest and is decompressed by use of gastric suction, the fluid balance is carefully maintained and sedatives given. When the patient recovers from the peritonitis, he is sent home with instructions to return to the hospital in 10 or 12 weeks for appendectomy.

Fifty cases of abscess were seen with four deaths. Abscess is best treated by drainage, care being taken not to break down the abscess wall as this might cause the infection to spread and produce fatal diffuse peritonitis.—Francis D. Murphy.

BABKIN, B. P., KOMAROV, O. AND KOMAROV, S. A.: *Endocrinology*, 26:4, pp. 703-716, April, 1940.

Clinical as well as experimental physiological literature appear to suggest that partial destruction of the parathyroid glands results in gastric hypersecretion and even in the formation of peptic ulcer. This, plus the fact that blood calcium plays an important role in regulating the excitability of the nervous system, (including presumably that part which controls the activity of the digestive glands) stimulated the authors to study the effect of activated ergosterol and of parathyroid hormone on gastric secretion in the dog.

Their findings indicate that: (1) activated ergosterol, when given daily to Pavlov-pouch dogs in doses sufficient

to raise the normal calcium content of the blood serum to 15.0 mg. per cent or higher, causes an inhibition of the nervous phase of gastric secretion provoked by meals of bread, milk and meat respectively, (2) the inhibition of gastric secretion develops gradually in proportion to the degree of hypercalcemia produced, (3) the chemical phase of gastric secretion is inhibited only slightly, if at all, and the gastric response to subcutaneous injection of histamine is in no way affected, (4) preliminary studies with daily administration of parathormone on gastric secretion in a dog with esophagotomy and a gastric fistula show that the volume of secretion (provoked by sham-feeding) and the total output of acid and of pepsin are diminished.

The authors stress that their data must be regarded as of preliminary nature. They state, however, that the following conclusions may be drawn: (1) the nervous phase of gastric secretion is the first to suffer as the result of repeated administration of activated ergosterol or parathormone, (2) ergosterol and parathormone do not act directly on the secretory cells in the way that histamine or some other chemical stimulants act, but through the nervous system—presumably through the parasympathetic system, (3) an important factor in the inhibitory influence of ergosterol and parathormone undoubtedly is the raised blood calcium concentration.

A very interesting and thought stimulating comment is made by the authors when they discuss the close relationship between parathormone, irradiated ergosterol and Vitamin D. They reason that if Vitamin D should influence gastric secretion, particularly its nervous phase, in the same way as irradiated ergosterol does, then the diet in ulcer patients ought to be properly balanced with respect to Vitamins D and B. Vitamin B (essential for normal gastric secretion) should be diminished and Vitamin D (if it inhibits secretion as does irradiated ergosterol) should be reasonably increased. This problem, they add, needs further investigation.—David J. Sandweiss.

SLEETH, CLARK K. AND VAN LIERE, EDWARD J.: *The Emptying Time of the Human Stomach After the Administration of Progestin*. *Endocrinology*, 26:3, pp. 535-536, March, 1940.

Progestin, a corpus luteum hormone, has been used in gynecological and obstetrical patients because of its inhibiting effect on the motility of the uterine musculature. Because of the fact that all investigations to date have been restricted to the action of the hormone on the uterus, the authors studied its effect on the emptying time of the stomach in the human in an effort to determine whether the corpus luteum extract might have some general action affecting smooth muscle in various parts of the body.

In four healthy young males the normal emptying time of the stomach was determined fluoroscopically after a meal of Farina, water and 50 gms. of barium sulphate. The effect of progestin was then determined by injecting each of the individuals with 1 cc. of progestin in oil, intramuscularly, twenty minutes before the intake of a similar meal. Each cc. of progestin contained one Corner rabbit unit in sweet almond oil. Several determinations at weekly intervals were made on each individual and the average was taken as expressing the emptying time of the stomach.

The authors found that there was considerable individual variation in the response to progestin. They were of the opinion, however, that the net result was a failure to influence the gastric emptying time of the subjects as a group. The net change of 2.4%, according to the authors, is within the range of the experimental error of the method. They state that "if it is permissible to use the smooth muscle of the stomach as the criterion, it appears that progestin has but little effect on smooth muscle other than that of the uterus." However, they suggest that in order to prove a definite specificity of progestin for uterine muscle, the effect of the progestin on smooth



muscle from various other parts of the body should also be studied.—David J. Sandweiss.

MCARDLE. *The Serum Choline Esterase in Jaundice and Diseases of the Liver.* *Quart. J. Med.*, Vol. 3, p. 107, Jan., 1940.

A study on 269 subjects revealed that an association exists between low serum choline esterase values and liver disease. Normal adults showed an esterase of 51 to 121 units (mean — 78) while in normal children (7 to 15 years) the serum esterase was 71 to 166 units (mean — 105). Where liver disease existed (hepatitis, cirrhosis, metastases in liver, hepatic jaundice) the choline esterase of serum in 79% of the cases was below 50 units (mean — 36). Patients with miscellaneous non-hepatic diseases yielded values of 13 to 138 units (mean—71). The author suggests that determinations of the choline esterase in serum may be useful in differentiating hepatic from obstructive jaundice since in the latter the values are above 50 units but in the former are below 50 units. A value below 50 units indicates that the liver has been damaged.—M. H. F. Friedman.

ALEXANDER, W. F.: *The Innervation of the Biliary System.* *J. Comp. Neurol.*, Vol. 72, p. 357, April, 1940.

The study is based on detailed dissection and examination of histological preparations of human and cat biliary systems. Extrinsic nerves arise from the right and left vagi and from the celiac plexus. In some the phrenic nerves play a limited role in the innervation. In cases of biliary disease, the referred pain in the area of distribution of the cervical nerves from which the right phrenic arises points to afferent phrenic nerve fibres distributed to the gall bladder. Small nerve ganglia, related to the parasympathetic nerves, exist in the hepatic portal and the walls of the gall bladder and cystic and common bile ducts. Within the liver structure no nerve fibres were observed. The intramural plexuses of the gall bladder and bile ducts, although less highly developed, are similar to the enteric plexuses and probably function in the same manner. By the technic of nerve section and degeneration it was found that the smooth muscle of the gall bladder and bile ducts is innervated by both sympathetic and parasympathetic nerves while the hepatic vessels are innervated solely through sympathetic nerves.—M. H. F. Friedman.

ROFFO, A. H.: *Malignant Tumours Developed in the Digestive Apparatus by the Ingestion of Fat Substances, Oxidized by Heating. Formation of Ulcers and Malignant Tumours in the Digestive Apparatus by Ingestion of Food with Irradiated Cholesterol.* (Spanish, English Summaries). *Bol. Inst. Med. Exper.*, No. 46, p. 589, and No. 48, p. 407, 1938.

Intense pathology of the digestive tract was found in rats which had been fed irradiated cholesterol-rich foods or else had had irradiated cholesterol added to the stock diets. The feeding of pure non-irradiated cholesterol was without effect. Erosions and round ulcers appeared in the stomach and these gradually developed into adenocarcinoma. Neoplasms of the liver were also common, the tumours formed having the structure of fusocellular sarcoma. The development of the pathological condition was slow and usually took 2 years. Similar results were obtained on rats receiving heated (oxidized) fats per os.—M. H. F. Friedman.

CHAIKOFF, I. L. AND CONNER, C. L.: *Production of Cirrhosis of the Liver of the Normal Dog by High Fat Diets.* *Proc. Soc. Exp. Biol. Med.*, Vol. 45, p. 658, April, 1940.

Well nourished dogs were fed twice daily a high fat diet, 10 gm. lard and 7 gm. lean meat per kilo per day. In ad-

dition bone ash, salt mixture and adequate vitamins were supplemented. Four dogs died after 138, 246, 298 and 386 days on the diet. The livers of 3 of the dogs showed severe diffuse fibrosis and all 4 showed severe fatty infiltration. No conclusions were drawn.—M. H. F. Friedman.

FELDMAN, M.: *Protrusion of the Appendiceal Stump Following Appendectomy.* *Radiology*, 34:571, May, 1940.

Feldman called attention to the clinical significance of protrusion of the appendiceal stump that may occur subsequent to appendectomy. The differential diagnosis of organic disease of the cecum is also discussed briefly. Two cases under discussion were encountered in a roentgenologic study (with the aid of a barium enema) in a group of 50 patients who had had an appendectomy. The defect is roentgenologically demonstrated by a nipple-like protrusion with a symmetrical indentation on each side of the nipple defect.—Robert Turell.

HATCHETTE, S.: *Multiple Diverticula of the Jejunum, Duodenum and Colon.* *Radiology*, 34:577, May, 1940.

The author presented roentgenologic evidence of an unique case of multiple diverticula of the duodenum, jejunum and colon. The diverticula of the duodenum and jejunum and their relation to other parts of the gastrointestinal tract were observed fluoroscopically during the progress of the barium meal in the intestinal tract. The roentgenographic examination also demonstrated the diverticula of the upper intestinal tract as well as those of the colon. A brief review of the literature dealing with diverticula of the upper portion of the intestinal tract is also given.—Robert Turell.

TEPERSON, H. I.: *Treatment of Carcinoma of the Rectum by Electrocoagulation and Radiation in Selected Cases.* *Radiology*, 34:610, May, 1940.

For 4 years, Teperson employed electrocoagulation followed by radium therapy in a group of 26 patients with advanced inoperable carcinoma of the rectum.

By destroying the tumor mass, a patent colonic tube was established and the need for a colostomy avoided. The author feels that electrocoagulation of the neoplasm followed by the application of radium has also an inhibiting effect upon adjacent metastases. The method of treatment by electrocoagulation and radiation is described in detail. Two men died within the first year, and three during the second year. One patient has been alive for over three and one-half years.—Robert Turell.

HOUGHIN, O. B. AND TURNER, C. W.: *The Relation of the Anterior Pituitary to Bile Production.* *Endocrinology*, 26:5, pp. 821-823, May, 1940.

Data in the literature appears to indicate that the anterior pituitary plays a role in fat metabolism, i.e., causing a fatty infiltration of the liver and a rapid decrease in the blood fat of the rabbit and guinea pig. Since bile is also known to regulate fat digestion, especially absorption, the authors felt that it would be reasonable to postulate that some anterior pituitary factor might influence the rate of bile production.

They therefore injected a series of 13 anesthetized guinea pigs, each weighing from 300 to 414 gm. with 25 mg. of anterior pituitary initial extract. They found a definite rise in bile secretion extending from 4-8 hours. The average hourly production of bile from 13 injected animals was 5.45 cc. as compared with an average hourly production of 2.94 cc. in 7 normal animals—an increase of 85%.

They are of the opinion that their data indicate that the anterior pituitary plays another role in fat metabolism in



addition to those mentioned above. "The definite increase in bile secretion is indirect evidence that the anterior pituitary is also concerned in the rate of fat absorption from the intestine."—David J. Sandweiss.

CATTELL, R. B. AND SWINTON, N. M. *Diagnosis and Treatment of Sigmoidal Polyps.* *N. Eng. J. of Med.*, 222: 535, March 28, 1940.

Ten cases of sigmoidal polyps are reported in which twelve polyps were removed. Five of the polyps showed early malignant changes. The authors believe that cancer frequently develops from benign mucosal polyps and therefore once the diagnosis is made the polyps should be removed by laparotomy. If there is no malignant change present in the base of the polyp radical resection is not indicated.—Henry H. Lerner.

ALLEN, A. W.: *Surgery of the Stomach.* *N. Eng. J. of Med.*, 222:434, March 14, 1940.

Preoperative preparation is extremely important since the character of the ailment often affects the ingestion and assimilation of proper food elements. In some instances a preliminary jejunostomy for feeding may be justified. Splanchnic block should be used for anaesthesia in addition to other anaesthetics in order to get complete relaxation. If the patient is uncooperative nitrous oxide and oxygen can be used. Spinal anaesthesia has been unsatisfactory in his hands. The technical procedures of operating for ulcer, gastrojejuno-colic fistula, polyps of the stomach, malignancy, leiomyoma and syphilis are discussed.—Henry H. Lerner.

JONES, CHESTER M.: *Gastro-enterology.* *N. Eng. J. of Med.*, 222:634, April 11, 1940.

A review of the literature for 1939 limited to the small intestine, the appendix, and ulcerative colitis.—Henry H. Lerner.

HORMELL, ROBERT S.: *Device for Ensuring Constant Gastric Suction.* *N. Eng. J. of Med.*, 222:759, No. 18, May 28, 1940.

An apparatus is described whereby the suction offered by the hospital vacuum system may be adapted to the Wangenstein Principle. By this method the suction is continuous and the amount of nursing care is minimized. The apparatus has been successfully used in thirty cases.—Henry H. Lerner.

LAHEY, F. H.: *Surgery of the Duodenum.* *N. Eng. J. of Med.*, 222:444, March 14, 1940.

At the Lahey clinic only 8.2 per cent of patients with duodenal ulcers have needed operation. The surgical trend has been toward resections. The surgical treatment of pyloric obstruction, perforation, hemorrhage and duodenal diverticulæ are described. Spinal anaesthesia with Nupercain is almost routinely used. The Finsterer operation of exclusion has been the method of choice with an antecolic enterostomy. An operative procedure is described which can be used with gastrojejunal ulcer, gastrojejuno-colic fistula, or with cancer high in the jejunum.—Henry H. Lerner.

GRINDLAY, J. H.: *Acid Secretion Following Procedures on the Pars Pylorica of the Stomach.* *Staff Meetings of Mayo Clinic Proceedings*, 15:225, April 10, 1940.

The author prepared a vagus denervated pouch of the fundus of the stomach in each of a group of dogs and studied the acid secretion from such pouches before and after operations in which the pars pylorica was either excised or removed from the gastric pathway. Three types

of operative procedures were carried out on the pars pylorica in different experiments on the above dogs:

1. The pars pylorica of the stomach was excised and the end of the remainder of the stomach anastomosed to the side of the first portion of the duodenum. This resulted in no important change in the acidity or quantity of the secretion from the fundic pouch.
2. In a second group of dogs the stomach was divided just above the pars pylorica, anastomosing the end of the body of the stomach to the side of the second portion of the duodenum, and closing the stump of the pars pylorica. The result of that operation was that the pars pylorica was merely removed from the gastric pathway. This resulted in a moderate increase in the volume and acidity of the secretion from the fundic pouch.
3. A second operation was performed on the dogs in group 2, i.e., the duodenum was divided just below the pyloric sphincter and the ends closed with inverting sutures, thus totally isolating the pars pylorica from the digestive tract. However, the pars pylorica remained within the peritoneal cavity as a pouch draining to the skin surface through a sinus in the abdominal wall or through a de Pezzer catheter. It was found that the volume, acidity and secretion curves were similar to those of group 2.—Thomas A. Johnson.

LAYNE, J. A. AND BOYDEN, E. A.: "Evacuation of the Gall Bladder in Patients with Pernicious Anemia." *Proc. Soc. Exp. Biol. and Med.*, 43, No. 3, p. 534, March, 1940.

Studies were carried out in 22 consecutive male patients in whom the diagnosis of pernicious anemia had been established. All were receiving liver therapy and the blood counts were either normal or approaching normal. All patients had an absence of hydrochloric acid even after histamine stimulation. In 40% of the patients the gall bladder could not be visualized even by intravenous cholecystography despite the absence of any clinical evidence of gall bladder disease. In the other patients the rate of emptying of the gall bladder approximated that of the normal controls. The authors conclude that the presence of free hydrochloric acid in the stomach is not an essential factor in the evacuation of the human gall bladder.—Henry J. Tumen.

BERMAN, A. L., SNAPP, E., HOUGH, J. S. AND IVY, A. C.: "Keto-Reacting Substances in the Bile of Dogs." *Proc. Soc. Exp. Biol. and Med.*, 43:547, March, 1940.

Previous workers have isolated and identified various ketonic acids in the bile from different animals but a quantitative method of determination was lacking heretofore. Such a method, newly developed, was utilized for the present study. Control investigations on bile from bile fistula dogs on a standard diet without the administration of bile or bile salts, revealed that keto-reacting substances were always present and were usually fairly constant in amount. The administration to these dogs of unoxidized bile acids (natural ox-bile salts) increased somewhat the amount of keto-reacting substances. A striking increase was seen after the administration of oxidized bile acids such as those contained in Dechacid, Ketochol and Decholin. This increase, however, is assumed to be due to recovery in the bile of the amount of keto-acid fed.—Henry J. Tumen.

WINFIELD, J. M.: "Effect of Whole Bile and Bile Salt of Swine on Gastric Motility of the Dog." *Proc. Soc. Exp. Biol. and Med.*, 43:474, March, 1940.

It has been previously noted that the feeding of dried whole bile relieved anorexia. This led to a study of the effect of bile on gastric motility. The gastric tonus and motility were measured in dogs with Carlson gastric

fistulae. When solutions of dried whole swine bile or sodium  $\alpha$ -glycohydrosesoxycholate were placed in the stomach during a quiescent phase contractions were produced. Their introduction during a contraction phase, however, usually produced inhibition of contraction. Introduction of plain water also occasionally produced inhibition. It is possible that the production of contraction in a quiescent stomach may explain the relief of anorexia by bile. The mechanism of the action is not clear.—Henry J. Tumen.

BORSON, H. J. AND METTHER, S. R.: "Relief of Hypochromic Anemia in Dogs with Synthetic Vitamin B<sub>6</sub>: Influence of "Filtrate Factors." *Proc. Soc. Exp. Biol. and Med.*, 43:429, March, 1940.

Four dogs maintained on a diet containing members of the B complex except B<sub>6</sub> developed hypochromic, microcytic anemia within 120-135 days. One dog was partially relieved by the addition of natural B<sub>6</sub> in doses of 60 micrograms/Kilo/day. Similar correction of the anemia was obtained in the other 3 dogs by the administration of the same dose of synthetic B<sub>6</sub>. In all cases a mild reticulocytosis followed the use of B<sub>6</sub>. In order to completely relieve the anemia produced by B<sub>6</sub> deficiency it was necessary to give adequate amounts of liver filtrate, containing non-adsorbable "filtrate factors." B<sub>6</sub> deficiency not only produces anemia but also weight loss, listlessness and asthenia.—Henry J. Tumen.

BRUNSWIC, A. AND SCHMITZ, R. L.: "Rapidly of Passage of Chloride Ion from Blood Into Gastric Juice of Stimulated Stomach." *Proc. Soc. Exp. Biol. and Med.*, 43:438, March, 1940.

Chloride ions were "tagged" by making them radioactive. Studies were carried out on two dogs with cannulated gastric pouches and in two patients by means of gastric juice aspiration. In the dogs and in man the "tagged" chloride ions injected into the general circulation appeared in the gastric juice in from 60 to 120 seconds. Such "tagged" chlorine ions remained in the general circulation for more than one hour and appeared in the gastric juice continuously during that time.—Henry J. Tumen.

FINE, J., FUCHS, F. AND MARK, J.: "Effect of Desoxycorticosterone on Plasma Volume in Intestinal Obstruction." *Proc. Soc. Exp. Biol. and Med.*, 43, No. 3, p. 514, March, 1940.

In control dogs it was shown that the longer the distention of the small bowel continued the greater was the loss of plasma. This averaged 35% after 4-6 hours and 55% after 18-23 hours. In four dogs receiving desoxycorticosterone it seemed that the hormone had the capacity to prevent loss of plasma and it was thought that desoxycorticosterone may counterbalance those changes responsible for plasma loss in intestinal obstruction. Although the use of this hormone at least partly prevented the decrease in plasma volume ordinarily observed in dogs continually subjected to small bowel distention, no prolongation of life occurred in the series of dogs studied.—Henry J. Tumen.

JELKS, EDWARD: *Massive Dilatation of the Common Bile Duct.* *Southern Surgeon*, 9:187-192, March, 1940.

Cystic dilatation of the common bile duct is generally regarded as congenital but has been described as idiopathic or acquired. It is more common in females and the etiology is unknown. The usual symptoms are recurrent attacks of jaundice, pain in the upper portion of the abdomen, and a palpable tumor occurring especially during childhood or early adolescence. However, jaundice, the most common symptom, is not always present. The most effective treatment is primary anastomosis to establish as early as

possible an adequate communication between the biliary tract and the intestine with the additional excision or partial excision of the cyst to reduce stasis.

A report is made of a two year old child who presented the usual symptoms. The palpable mass which extended below the enlarged right lobe of the liver was longitudinal rather than transverse, was about 2½ or 3 inches wide, not tender but fairly well fixed to the deep structures. Urography showed the kidneys normal but the bladder surface altered. At operation the mass was incised but the ampulla of Vater could not be demonstrated. The mass was anastomosed with the duodenum. At autopsy no normal communication was found between the duodenum and the cystic enlargement which was taken to be the dilated common bile duct and no communication between the ampulla of Vater and the extrahepatic bile ducts was found but the hepatic duct did open into the sac just beyond the neck of the gall bladder.—J. Duffy Hancock.

MOONEY, J., JR.: *The Atypical Signs and Symptoms in Perforated Peptic Ulcer.* *Southern Surgeon*, 9:179-186, March, 1940.

Twenty to thirty per cent of perforated ulcers come to operation incorrectly diagnosed because they do not present the usual well-recognized signs and symptoms. This variation may be due to a number of causes. The pain may be accentuated by irritant intragastric contents, a small amount of spillage may limit the signs to a localized area, an ulcer on the anterior superior surface may direct the fluid to the right gutter and simulate appendicitis, one on the posterior wall will rupture into the lesser peritoneal cavity and cause colicky pain like that of obstruction, ulcers on the greater and lesser curvature and at gastrojejunal anastomoses will cause pain and rigidity in the left abdomen, and frequently after a few hours the initial severe pain temporarily subsides. This latter is especially true in the subacute or plugged perforations.

However, in doubtful cases as well as the easily diagnosed, there are two cardinal symptoms, the onset of sudden sharp pain in the epigastrium and, due to gravitation of the spilled fluid, bilateral tenderness on rectal examination. These two findings should suggest the diagnosis. Shifting of pain in old gastric or duodenal ulcers should lead to the assumption of deep penetration or partial perforation.

Two atypical cases are reported—one simulating acute appendicitis and one intestinal obstruction.—J. Duffy Hancock.

ZISKIND, JOS AND SCHATTEBERG, H. J.: *Left Paraduodenal Hernia.* *Southern Surgeon*, 9:175-178, March, 1940.

Paraduodenal hernias are located about the duodenojejunal flexure, and are composed of small intestine protruding through a congenital or anomalous opening which is entirely within the abdomen. In the more common left paraduodenal hernia the sac is situated to the left of the ascending colon and is suspended from the transverse colon and mesentery—in the right paraduodenal hernia the sac is situated to the right of the ascending colon. While the hernias are usually post natal in origin it is possible that their development is based upon embryonic anomaly. The amount of contained small intestine is variable but the finding of omentum within the sac has not been reported.

Autopsy findings of an unsuspected left paraduodenal hernia with its opening pointed to the right are described.—J. Duffy Hancock.

PHILLIPS, J. R. AND KNOEPP, L. F.: *Surgical Management of Biliary Tract Disease.* *Southern Surgeon*, 9:153-168, March, 1940.

Increased knowledge of the physiology of the biliary system and technical advances in operative procedures

account for the improved results in biliary surgery. Impaired function of the gall bladder should necessarily imply a thorough study of the entire biliary tree and pancreatic ducts. The usual pain and tenderness are well understood. Positive cholecystograms are of great importance but many gall bladders reported as normal will show definite disease at operation. Important laboratory aids are the Van den Bergh reaction, galactose tolerance test, bromsulphthalein liver function test, quick hippuric acid test (an excellent index as to detoxifying powers and possibility of liver deaths), quantitative fibrinogen studies, quantitative blood iodine, clotting tests, estimations of bile in the urine, urobilinogen, analysis of stools, icterus index, blood amylase, etc.

Operation is advised in all stone cases, for cholecystitis even when there is some doubt about the diagnosis, acute cholecystitis in the first three days of the disease, or after clinical improvement in the delayed acute cases. The elderly and hypertensives are good risks if the cardiovascular-renal reserve is adequate.

Pre-operative measures advocated are glucose, fluids 3500 to 4500 cc. a day, bile and Vitamin K to correct prothrombin deficiency, and oxygen in jaundiced cases. The Kocher-Mayo incision and thorough exploration are recommended. Cholecystectomy is preferred, reserving cholecystostomy for those cases where the inflammatory process is so acute the gall bladder cannot be safely shelled out or where the gall bladder may be needed later for short-circuiting. Exploration of the common duct is indicated if dilatation is present and should be done through a separate opening rather than the stump of the cystic duct. Drainage of the peritoneal cavity is almost always employed.

Post-operative treatment consists in a continuation of the pre-operative measures plus the Trendelenburg position, carbon dioxide inhalations, intratracheal suction and even bronchoscopy for chest complications. The T-tube should not be removed until the ducts are patent and the bile approximately normal.

Sixty-seven cases with a gross mortality of 7.5 per cent are analyzed.—J. Duffy Hancock.

GAGE, MIMS: *Pre-operative and Post-operative Use of Drugs in Surgery of the Gastro-intestinal Tract. Southern Surgeon, 9:149-157, March, 1940.*

There are many drugs useful in pre-operative, operative and post-operative periods. Fluids, glucose and blood are especially important before operations and are the fundamentals for proper preparation of patients. Other drugs and measures have more specialized indications. Pre- and post-operative purgation are undesirable. Pre- and sedation is of considerable importance. The anesthetic should be selected in consultation with and be administered by a specialist. Stimulating drugs of the epinephrin group will seldom be needed during operation if the patient is maintained in physiological balance by the intravenous administration of fluids and blood when indicated. Post-operatively drugs are indicated for the relief of pain, cerebral excitement, or intestinal atony. The pain (and cerebral excitement) is best controlled by morphine or one of the other opiates, ileus by morphine and the physostigmine group.—J. Duffy Hancock.

BARTLETT, M. K. AND MILLER, R. H.: *Acute Appendicitis as a Complication of Carcinoma of the Cecum. N. Eng. J. of Med., 222:783-784, May 9, 1940.*

Two cases of carcinoma of the cecum complicated by acute appendicitis are added to the six cases previously reported in the literature. It is noted and emphasized that a definite acute appendix may obscure the presence of an underlying carcinoma which may be overlooked at time of operation.—Henry H. Lerner.

JONES, C. M.: *Surgery of the Stomach and Duodenum, Medical Aspects. N. Eng. J. of Med., 222:425, March 14, 1940.*

Dr. Jones states that relatively few gastric and duodenal ulcers are cured. Because of the recurrence of the disease it should be considered as one that requires continuous management. Recurrences are due to irregular habits of living and eating, infection and emotional disturbances.

There is a definite trend toward medical therapy in the handling of this disease except in well planned cases where surgery is indicated. About twenty per cent of all cases need surgery. The indications for this are acute perforation, complete pyloric obstruction, hemorrhage, failure of medical treatment, gastrojejunal ulcer and gastric ulcer about the nature of which there is some question. He advocates the use of transfusion during hemorrhage.—Henry H. Lerner.

MALLORY, TRACY B.: *Pathology. New Eng. J. of Med., 222:925, 1940.*

In reviewing catarrhal jaundice the author notes one paper in which thirty-eight aspiration biopsies were made, the findings showed a diffuse hepatitis which in three cases showed an increase in connective tissue suggesting cirrhosis and in one instance subacute atrophy developed. A new suggestion as to etiology is suggested from the fact the hogs in Denmark frequently suffer from jaundice with the same seasonal variations that humans do. Bile obtained from patients with catarrhal jaundice produces jaundice in young pigs.—Henry H. Lerner.

MOORE, GEORGE A.: *Appendices Epiploicae. New Eng. J. of Med., 222:919, 1940.*

Briefly reviewing the literature the author notes numerous instances where pathological changes of the appendices epiploicae produce symptoms which may require abdominal exploration. Torsion was the most common cause. It may be acute or chronic. Often such cases give a history of frequent episodes. The author adds two cases of torsion, one case of herniation, and two cases of strangulation of the small intestine as a result of a fibrous band following involvement of the appendix epiploica.—Henry H. Lerner.

GAIRDNER, DOUGLAS: *The Association of Gall Stones with Acholuric Jaundice in Children. Report of a Case in a Child Aged Three Years with a Note on the Crisis of Acholuric Jaundice. Arch. Dis. Childhood [London] 14(78):109-120, 1939.*

Gairdner reports a case of gall stones with acholuric jaundice in a 3 year old child. Splenectomy and cholecystectomy were performed and the child recovered. Gall stones are probably more commonly associated with acute hemolytic icterus, than is generally recognized.—D. J. Pachman (Courtesy of Biol. Abst.).

FUCHS, HEINRICH: *Zur Kenntnis der Zusammensetzung der Magenschleimhaut. Zeitschr. Biol., 99(5):484-487, 1939.*

Arginin, lysin, tyrosin, leucin and histidin were found free in the pig's gastric mucosa; likewise nicotinic acid or the acid-amide, the presence of which can explain the effect of adm. of the membrane on pellagra. Histamin in the amount of 0.6 mg./100 g. fresh mucous membrane was determined by test with guinea-pig intestine.—F. H. Pratt (Courtesy of Biol. Abst.).

SCHINDLER, RUDOLF AND BAXMEIER, ROBERT I.: *Mucosal Changes Accompanying Gastric Ulcer: A Gastroscopic Study. Ann. Int. Med., 13(4):693-699, 1939.*

91 patients having a gastric ulcer were examined gastroscopically, many of them repeatedly. No inflammatory

changes of the mucosa were found in 3 patients. Ulcerative antrum gastritis was never observed. These findings do not agree with the observations of European pathologists or with the theory of the gastritic origin of chronic gastric ulcer. Purpuric type changes, mucosal hemorrhages, pigment spots, hemorrhagic erosions were seen in 40 patients. The high incidence of these lesions in the ulcer-bearing stomach may have some significance.—R. Schindler (Courtesy of Biol. Abst.).

VAN LIERE, EDWARD J. AND SLEETH, CLARK K.: *The Effect of Fluidextract of Ergot and of Ergotamine on the Emptying Time of the Human Stomach.* J. Pharmacol. and Exp. Therap., 67(2):250-255, 1939.

The normal gastric emptying time was determined fluoroscopically in 9 healthy young adults. The test meal consisted of 16 g. of Quaker Farina. Two cc. of fluid-extract of ergot caused an average delay of 29.9% in the gastric emptying in 9 subjects. One mg. of ergotamine caused an average delay of 16.4% in 7 subjects. The fluid-extract had a more pronounced effect than ergotamine because the former contained all the alkaloids of ergot, some of which were stronger in their action than ergotamine, and the dose of the fluidextract was more active than was the dose of ergotamine. The delay in gastric emptying produced by the ergot preparations was evidently due to direct inhibitory action on the gastric musculature.—E. J. Van Liere (Courtesy of Biol. Abst.).

## CONNOTATIONS

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The origin of iron therapy is lost in ancient history. Many references are made to its use in biblical times. It was used in China and Egypt in 3000 B.C. Pliny, born 23 A.D., whose writings contained a mass of information on physics, astronomy, fables and facts, regarded iron rust as a most valuable remedy for the undernourished. Its mode of administration is more interesting than its historical introduction. The wearing of amulets around the extremities and genitalia was common and in extreme cases the head was shaved and upon it a flat piece of iron was placed. In this manner it was believed that iron was absorbed and imparted strength to the blood. Dried blood was mixed with many ingredients such as fats from various animals and powdered bones. Dried blood added to the fat of eunuchs was thought to be very beneficial. Blood mixed with the dung of crocodiles, powdered bones from mummies, and menstrual blood was eaten at the discretion of the individual. Mummies were actually imported from Egypt for this purpose. Following a severe loss of blood, Richelieu, a famous French statesman who lived 1585-1642 took freely of a decoction made by dissolving horse dung in wine.

In 1766, Hillary described a condition which he termed *aphthoides chronica*. In 1880, Sir Patrick Manson gave the disease the name of sprue. Before the time of Hillary, John Brickel, a physician in Dublin, described the same condition under the name of white flux.

In 1899, Meltzer of New York, called attention to a fact that paralysis in rabbits occurred after intracerebral injection of magnesium sulphate. At a later date, he persuaded Dr. Haubold at the Harlem Hospital, Dr. Willy Meyer at the German Hospital, and Dr. Joseph Blake at the Roosevelt Hospital to induce anesthesia by injection of a solution of magnesium sulphate in the spinal canal. In Dr. Blake's case, appendectomy was performed two hours after injection. The patient remained comatose for sixteen hours. No evidence of sensation could be obtained for twenty-eight hours. In 1904, Dr. John B. Murphy advised intraspinal injection of magnesium sulphate for

tetanus because of its inhibiting both afferent and efferent nerve impulses.

Dioscorides, a Greek Army Surgeon under Nero, was the founder of materia medica. No attempt was recorded to improve it. Approximately ninety drugs he mentioned find a place in the pharmacopeia.

Aristotle, a pupil of Plato, gave the first information on embryology of the chick's heart. He also coined the term, *aorta*.

Behring, who discovered antitoxin, was not a physician and neither was Pasteur.

Reil is considered the actual founder of psychiatry. He demonstrated that definite areas in the brain controlled certain portions of the body. In 1805 he established a journal dealing entirely with mental diseases.

During the nineteenth century, Heinroth's knowledge of mental disease was associated with Biblical teachings. He taught that madness represented sin and that mental health depended upon an individual's reverence toward God.

The term, *Mesmerism*, is derived from Franz Anton Mesmer, who was an imposter. His demonstrations appeared in public. His patients joined hands around a chaldron and each was touched with his magic wand. In 1841, Braid introduced the term *hypnotism*.

Aristotle who lived 322-384 B.C., in his writings states that man has more teeth than woman and that this difference exists in other animals.

In 1862, J. Martin Charcot established the greatest neurological clinic of his day at Salpêtrière. He discussed the organic point of view of nervous manifestations.

The word *purpura* is derived from a Greek word designating a purple fist. For many years, the term was used to denote any eruptive purple discoloration. It was for a time classed or confused with measles. During the year 1700, a few observers noted the presence of purpura in the absence of fever; this necessitated its removal from the exanthemata class and restricted its use.

In 1690, which was thirty-five years after Mayerne's death, a posthumous edition of his case records were collected and published under the name of *Praxis Medica*; they comprised twenty-three volumes. Concerning the treatment of epilepsy, he advised the use of one dram of dung from a white peacock, dissolved in four ounces of wine; this remedy was also a favorite for anemia. He must have considered the light of the moon as an aid in treatment as epileptics were considered lunatics (derived from *luna*, meaning the moon). Regardless of his thought, he advised that the decoction be given four hours before dinner on the last day of the full moon.

Aspasia, a woman physician who lived during the second century A.D., limited her practice to gynecology and obstetrics. She discussed the treatment after removal of a dead fetus, suppressed menstruation, prenatal care, malpositions of the uterus, sterility, and methods of preventing conception. In order to induce a necessary abortion, she advised the patient on the thirteenth day following her missed menstruation to be subjected to violent exercise, lifting of heavy objects, hot douches, hot sitz baths, poultices to the abdomen; she also advised drinking of large quantities of tea and infusions from herbs. The fetus was supposed to be dead at the end of the fourth month; at this time the patient would abort.

Henri de Mondville, who died in 1320, published a text book of anatomy. The chronological arrangement of his text was similar to preceding anatomists. He believed the human skeleton consisted of 202 bones and 75 nerves. He described the female breast as composed of veins, arteries and spongy flesh; within the spongy flesh were numerous cavities filled with soft white flesh in which milk was formed. He stated the breasts and uterus were connected with veins. This concept arose probably from an old belief which in effect stipulated that food for a new-born infant

should not differ from that provided for the uterus. The result of such reasoning led to the belief that menstrual blood was carried to the breasts and transformed into milk. Considerable importance was attached to the location of the breast for various reasons. They were near the heart so that they could easily be warmed; their thickness maintained natural heat to the thorax and thus warmed and strengthened the stomach.

Mondino de Luzzi, who died in 1326, in his text book on anatomy, according to Pilcher, gave directions for closing wounds in the intestine. The lips of the wound were to be drawn together and large ants were forced to bite through the approximated edges. The head of the ants were then to be decapitated.

Jacob Berengario da Carpi was professor of Anatomy at Bologna. He first described anastomoses between the portal vein and the inferior vena cava. His description of the thymus, seminal vesicles, and the arytenoid cartilages of the larynx was fairly accurate. He denied the existence of a middle ventricle of the heart and the existence of a multiple chamber in the uterus, a theory in vogue at that time.

Nicholas Massa was the first anatomist to give a fairly accurate description of the prostate gland. He died in 1569.

Mrs. George Washington's only daughter, Patsy, was an epileptic. In 1769, Mrs. Washington permitted Patsy to wear an amulet of iron to forestall future attacks. George Washington's reply to suggestion of Colonel Lear that he take medicine for a cold was: "Let it go as it came." It is recorded that he contracted the cold which led to his death in December, 1799, on his return from one of his nightly concubinal visits.

Thomas Willis, who lived 1621-1675, described the circle of Willis and taught that the cerebellum was the center of vital activities. He described certain clinical conditions now recognized as paresis. He also reported a case of cardiospasm in 1672.

Dr. Guillotin, a practitioner of Paris, became exasperated at the cruel method of executing criminals; he believed that too much distinction in capital punishment was drawn between the common people and aristocrats. He proposed in 1789 a machine known as the guillotine that all might be subjected to similar treatment. Sheep and dead criminals were used to determine the degree or angle the knife should be set. The first victim was a street robber who was detained for two months until the machine was perfected.

Sprays in the treatment of throat and nose diseases were devised in 1872 by an American named Sass. A nasal saw for removal of septal spurs was devised by an American pioneer in rhinology in 1881.

Green of New York, in 1842, was one of the first to successfully introduce drugs into the larynx. He was a prolific writer. In 1849 his text on pathology and treatment of croup appeared. Three years later an article on the surgical treatment of polypi of the larynx and edema of the glottis was published. In 1846 he edited a text book on diseases of the air passages. In this edition he described the methods of direct application of drugs to the vocal cords and the removal of laryngeal growths. The profession here and abroad accepted his statements with doubt, but so great was criticism among his colleagues that he was rejected from the medical society. He is now credited as the father of laryngology in America.

Mesue, who lived 777-837, wrote the *Antidotarium*, an essay covering what was known of common diseases and their treatment. His teachings remained prevalent for over two hundred years. He mentions the use of an anesthetic sponge which he named *consolation*. The sponge was soaked in a boiling concoction composed of mandrake, vinegar and poppy juice, and the patient was instructed to inhale the vapors. He recommended this as a remedy for relief of pain and especially for a woman in labor.

Phazes, an Arab who lived from 860-932, is thought to be the first to recognize measles and smallpox. He distinguished them from other eruptive diseases. He governed the sixty hospitals in Damascus, but in spite of his acumen as a diagnostician, died blind and in poverty.

An Anglo-Saxon *Materia Medica* appeared in 900 A.D. It was known as the *Leech Book of Bald*. Whether Bald was the author or an anonymous name is not known. The word *Leech* was an old name for doctor. The use of drugs, their indications and formulas were all legendary. As an example: The name of Lazarus was written in wax and tied to the bottom of one of the feet of a mother in labor. It was thought to shorten the time interval because Lazarus came quickly out of the tomb when called. The use of drugs was associated in all instances with holy water, prayers, or other magical phenomena.

Dr. Philip Madison Shepard founded the first medical school of Alabama in 1852. During the first three years of its existence he taught all the classes. His oldest son, John, was placed on the faculty at the age of eighteen. Three years later a second son joined the faculty. In 1860 the third son became Professor of Obstetrics. His daughter was graduated from her father's institution but did not undertake the practice of medicine. She probably was the first woman of the South to be honored with a medical degree. Shepard in a controversy with colleagues over the cause of death of a negro woman exhumed the body and performed an autopsy in the presence of his students. His finger was accidentally cut during the autopsy procedure, septicemia developed, and death followed within a few days.

BESREDKA, A., ET GROSS, L.

*Epithelioma Experimental de l'estomac. Immunisation par voie Intracutane.* Ann. Inst. Pasteur [Paris] 62(3):253-259, 1939.

The rabbit stomach shows a marked receptivity for the epithelioma of Brown-Pearce. A short period of incubation precedes the appearance of the epithelioma of the stomach which manifests itself by a tumor, more or less voluminous, localized at the point of inoculation. In nearly half the cases, the tumor is accompanied by metastases in the internal organs. Rabbits which had absorbed tumors inoculated intracut. showed a solid immunity against tumors inoculated into the stomach.—H. Pettit (Courtesy of Biol. Abst.).

MEISELAS, DAVID A.

*The Prognostic Value of Cholesterol Partition Study.* Rev. Gastro-enterol., 6(5):441-443, 1939.

Persons with degeneration of the liver show marked lowering of cholesterol esters in relation to cholesterol.—G. H. Chapman (Courtesy of Biol. Abst.).

LOEWENBERG, SAMUEL A.

*The Anemias Versus Gastro-Intestinal Disease.* Rev. Gastro-enterol., 6(5):402-411, 1939.

A brief discussion of the relationship between gastrointestinal diseases and various anemias.—G. H. Chapman (Courtesy of Biol. Abst.).

LOZINSKY, E. AND GOTTLIEB, R.

*Substitute for Bile Salt for Administration with Substances Possessing Vitamin K Activity.* J. Biol. Chem., (Baltimore), 133:635, April, 1940.

Vitamin K and substances possessing Vitamin K activity are absorbed from the gastro-intestinal tract only in the presence of bile or bile salts. If this is due to a non-specific factor of high surface-activity a substance such as dioctyl sodium sulfosuccinate which is non-toxic and highly surface active would promote absorption of 2-methyl-1, 4-naphthoquinone equally as well as bile salts. This was subjected to experimental test and found to be the case.—Ira A. Manville.

# Analysis of 256 Gastrosopies Performed at Bellevue Hospital\*

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**I**N the past nine months 256 examinations with the flexible gastroscope (1) were performed on 237 patients at Bellevue Hospital. Chronic gastro-intestinal complaints in all patients and onset of digestive symptoms in patients over forty-five years of age were considered to be indications for gastroscopy.

Table I shows the incidence of the various lesions encountered in our series. Chronic (superficial, atrophic or hypertrophic) gastritis was included in the diagnosis even though it was a finding associated with the primary diagnosis of ulcer, carcinoma, or a more prominent form of gastritis. When the secondary diagnosis of gastritis was excluded, the figures still show a 50% incidence. The clinical significance of gastritis with consideration of certain etiological and therapeutic measures will be considered in a subsequent paper. It is worthy of note at this time, however, that severe hypertrophic gastritis was the most common type found in patients who had been subjected to gastric surgery and those having partially resected stomachs showed less pronounced changes than when gastro-enterostomy was performed.

In sixteen cases of gastric ulcer seen, corroborative roentgenological evidence was present in fifteen, and operative confirmation was obtained in three patients. Two gastro-intestinal series failed to demonstrate two ulcers which were twice seen on gastroscopic examination. The ulcers were on the lesser curvature, one appearing on the angulus, and the second about three centimeters above. They appeared shallow through the gastroscope, but were still present on the second examination nineteen days later. In another case X-ray diagnosis of duodenal ulcer and large ulcer of the posterior wall of the stomach was made. On gastroscopic examination the large posterior wall ulcer was seen as well as a smaller ulcer directly opposite on the anterior wall. Operation revealed both gastric ulcers with scarring of the duodenal bulb from previous ulceration.

On six occasions X-ray diagnosis of ulcer was made when gastroscopy failed to demonstrate the lesion. In two patients the scar of an old ulcer was seen at the site described by the roentgenologist, and superficial gastritis was found to be present. Two patients had ulcers on the lesser curvature of the antrum, which could not be visualized, and another an ulcer of the lesser curvature of the body, near the posterior wall, which was not seen by gastroscopy, but confirmed by operation.

In the twelve patients in which the diagnosis of malignant lesions of the stomach was made, in only

two was the lesion subsequently demonstrated to be benign in character. One of these presented a dead-white appearance with fiery red streaks on gastroscopic examination, and the entire mucosa appeared stiff and the stomach was difficult to inflate. Diagnosis of diffuse carcinomatous infiltration was also made by X-ray. At operation the stomach appeared normal but histological examination revealed a diffuse infiltrative gastritis. The patient was luetic and had received specific therapy which has been continued since operation. The patient is now ambulant and has survived for six months. In the other instance a stiff, fixed deformity of the angulus and a small rigid pyloric opening suggested the gastroscopic diagnosis of malignancy. X-ray examination had revealed a greatly shortened lesser curvature with a fixed narrowing of the pyloric canal, also suggesting the diagnosis of possible malignant infiltration of the antrum. On operation the lesser curvature of the antrum was greatly shortened by scar tissue, which extended in a linear fashion down the anterior wall and caused the deformity of the angulus. A large ulcer with a hard fibrotic base and margins was present on the lesser curvature of the antrum. This was in one of the recognized blind spots for the gastroscopist. The freshly resected pylorus revealed a greatly thickened sphincter and the opening was so small that a one centimeter diameter probe could be introduced only with force. Histological examination showed the lesion to be a benign ulcer with extensive scar formation.

On five occasions the gastroscopic diagnosis of gastric carcinoma proved to be an important supplement to X-ray findings. One of these patients had been unsuccessfully X-rayed because of weakness, but a later attempt resulted in a report of a normal stomach with ulcer of the first portion of the duodenum. Gastroscopy revealed a necrotic, bleeding ulceration on the posterior wall near the cardia, which was considered to be malignant. The patient was transferred to a home for chronic diseases and six months later gastroscopic examination and X-ray revealed a mass in the stomach. In the second of these cases, X-ray reported a persistent defect in filling of the gastric fornix, indicating neoplastic infiltration, while on gastroscopic examination a large, irregular, bleeding, well circumscribed mass was found on the greater curvature at the fundus, and an area of thin mucosa was observed opposite this lesion on the lesser curvature near the cardia. The mass was again seen one month later. The patient's general condition did not permit operation. He was transferred to a hospital for chronic diseases from which he signed his release three months later even though he was still bedridden.

In another instance X-ray reported normal stomach and duodenum, while gastroscopic examination re-

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vealed a large nodular mass on the greater curvature near the fundus. At operation the mass was found with metastases to the liver and lymph nodes. The fourth case was thought to have neoplastic involvement of the stomach on first X-ray examination. A repeat examination four months later described a marked incisura of the greater curvature of the body of the stomach with ulceration of the opposing lesser curvature. Gastroscopy at this time revealed a finger-like protrusion from the posterior wall of the body of the stomach with a reddened irregular infiltration at the base. A diagnosis of gastric carcinoma was made.

TABLE I

Gastroscopic Findings	%	No. Pts.	%	No. Pts.
Normal	22.2	222	24.4	58
Mucosal, hemorrhages, hemorrhagic erosions, pigment spots	5.6	56	9.2	22
Gastric ulcer	7.1	71	6.7	16
Sequelae ulcer	1.4	14	2.1	5
Chronic nonspecific gastritis (total)	41.8	418	59.8	142
A. Chronic superficial	11.0	110	29.1	69
B. Chronic atrophic	13.6	136	17.7	42
C. Chronic hypertrophic	17.2	172	13.0	31
Gastric syphilis	0.3	3		
Gastric lymphogranuloma (Hodgkin's)	0.2	2		
Benign tumors	2.2	22	1.2	3
Gastric carcinoma	7.7	77	5.0	12
Lymphoblastoma	0.1	1		
Congenital diverticulum	0.3	3		
Diaphragmatic hernia	0.2	2		
Post-operative stomach	8.0	80	6.7	16
Accidents	0.3	3	0	0
Examinations attempted but not successful	1.4	14	2.5	6
Examinations made but not satisfactorily	1.2	12	5.0	12

Laparotomy revealed a mass high up in the stomach with metastases to the liver.

In the fifth case the patient had been operated on for the perforation of an ulcer on the greater curvature of the antrum, five months before. The diagnosis at that time had been 'benign ulcer' with perforation and simple closure was done. On the patient's readmission to the hospital, X-ray examination revealed a filling defect at the site of the former closure. The possibility of neoplastic changes was suggested, but the differential diagnosis could not be made from a simple infolding of the mucosa at the previous oper-

ation. Gastroscopy revealed a nodular bleeding mass protruding into the lumen of the stomach and extending across the greater curvature, limiting the antrum. The floor of the antrum was gray and nodular and a black suture was evident. Diagnosis of carcinoma of the antrum was made. Operation and histological study confirmed this diagnosis.

On one occasion roentgenological examination suggested carcinoma of the pyloric antrum. Gastroscopic impression was that of normal stomach. Repeat examinations by both procedures resulted in the same divergence of opinion. The patient has no anemia, weight loss, or digestive disturbance. Free hydrochloric acid was present in his gastric secretion and he has continued in good health for eight months, but is still under observation. A similar problem occurred in a young man following complete colectomy for ulcerative colitis. X-ray revealed a scalloping of the greater curvature of the body of the stomach, which was interpreted as being a carcinomatous infiltration. Gastroscopy revealed a normal gastric mucosa. The patient has continued in good health for seven months.

Mucosal hemorrhages were found in two patients to account for previously unexplained hematemesis. In one of these cases the gastric mucosa was markedly atrophic and was studded with yellow nodules one-half centimeter in diameter. The bleeding area was found on the posterior wall. This patient had pulmonary tuberculosis and a tentative diagnosis of gastric tuberculosis was made. Operative confirmation of this diagnosis has not been obtained, but the patient is being followed.

The small benign-appearing nodules seen in three patients could be demonstrated by X-ray in only one case. These lesions, according to Schindler (1), are usually benign fibromata, and were found in the antrum in all instances. None of these patients have come to operation or autopsy but are under observation.

#### SUMMARY

Gastroscopic findings of 256 examinations performed on 237 patients are recorded and discussed. The incidence of various lesions as described by Schindler are found to closely approximate his percentages. The analysis of the results further emphasizes the importance of gastritis in patients with chronic gastro-intestinal complaints. This finding is particularly important in explaining the persistence of symptoms post-operatively. The contributions obtained from gastroscopic examination in patients in the cancer age makes its inclusion imperative in the routine diagnostic study of this group.

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# The Management of Acute Cholecystitis\*

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THE management of acute cholecystitis occupies today approximately the same position occupied by the management of acute appendicitis some 40 years ago. Opinion, both medical and surgical, is widely split into essentially two schools: one, demanding that acute cholecystitis be considered as an intra-abdominal surgical emergency requiring operation as soon as possible; the other, contending that in most cases the disease will subside and that operation should be postponed until the interval or chronic stage after subsidence has occurred. It is the purpose of this presentation to review the arguments and the results

(1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16). In over 92 per cent of cases the obstructing agent is a calculus impacted at the neck of the gall bladder (Table I). The association between acute cholecystitis and impacted calculi is even more striking when it is noted that at the Mayo Clinic between 1935 and 1938 there were only 8 cases without stones (17). Furthermore, 6.4 per cent of the cases of common duct stones encountered at the Mayo Clinic revealed no stones in the gall bladder (18). In some instances, then, in which the gall bladder is found not to harbor stones after an attack of acute cholecystitis, it is probable that a stone was present but was expelled into the common duct.

The obstruction closes off the egress of bile, causes an accumulation within the gall bladder of its normal secretions, and thereby a gradually progressive distention of the organ. As the distention proceeds the vessels and lymphatics in the wall are compressed and pressure is exerted on the rich vascular plexus about the cystic duct. On the latter, in addition, is exerted the pressure effect of the edema about the site of obstruction and, possibly, pressure from the impacted calculus itself. As a consequence of these various changes, the vascular supply to the gall bladder is injured and there may then follow ischemia of the wall, necrosis, gangrene or perforation.

Despite the experiments and teachings of Rosenow (19) and Rehfuss (20, 21) it is agreed by the majority of workers today that infection plays but a secondary role to the primary ischemia in the pathogenesis of acute cholecystitis (1, 6, 8, 9, 13, 22, 23, 24, 29). Damage to the gall bladder or interference with its blood supply has been demonstrated as a prerequisite to the production of experimental cholecystitis (25, 26). Histopathologic studies of the gall bladders in acute cholecystitis have failed to reveal infectious lesions (6, 9, 13). Microscopic examination of the gall bladder fluid shows a paucity of white blood cells (6, 9, 13, 29), and in the opinion of Andrews the exudate in what is commonly termed "empyema" is really, in many cases, precipitated calcium carbonate and cholesterol. Although positive cultures are more commonly obtained in acute cholecystitis than they are in chronic cholecystitis (15, 27, 28, 29), the average findings in large series of both types yields positive cultures in no greater than 35 per cent (13, 22, 23, 24). Furthermore, Bockus, Willard and Metzger (24) secured their greatest percentage of positive cultures in non-functioning gall bladders and concluded that infection was secondary to an obstruction from a calculus.

The time necessary for these changes to appear after a stone has become impacted will vary with the completeness of the obstruction and with the anatomical arrangement of the blood vessels in the individual case. Evidence of gangrene in patients operated on within 48 hours after the onset of acute

TABLE I  
Incidence of gall bladder stones in cases of acute cholecystitis

Author	Year	Cases	Number with Stones	Per Cent
Baumgartner (48)	1929	319	308	96
Pratt (49)	1933	45	41	97.7
Lipshutz (4)	1935	20	19	95
Taylor (30)	1936	129	122	94
Wolfson and Rothenberg (50)	1936	1221	1122	91.9 (average)
Branch and Zollinger (31)	1936	229	214	93.4
Walters (2)	1937	76	72	94.7
Kunath (35)	1937	90	83	92
Totten (47)	1938	100	75	75
Pennoyer (43)	1938	274	268	98
Graham, R. H. (14)	1939	63	56	88.8
Branch (16)	1939	92	92	100
Carter, Greene and Twiss (54)	1939	574	511	89
Bettman (11)	1939			100
Walters and Snell (17)	1940	508	484	95
Cutler and Zollinger (7)	1940	123	115	93.5
Bockus (8)	1940			90.4
Average		3863	3575	92.5

advanced by both sides and from these to justify an individualized, liberal, middle-of-the-road attitude.

It is a prerequisite to the evaluation of any proposed plan of treatment to first appreciate something of the pathologic-physiology of the condition to be treated.

**Pathogenesis.** There is today almost universal agreement that acute cholecystitis is primarily dependent upon an obstruction to the outlet of the gall bladder

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TABLE II  
*Clinical course of acute cholecystitis*

Author	Year	Cases	Period of Observation	Improved or Subsid	
				No.	%
Love (52)	1929	69		60	87.0
Zinninger (53)	1932	54	1-12 days	20	37.7
Taylor (30)	1936	129	2 days	49	37.9
Kunath (31)	1937	49	7.6 days (average)	32	65.3
Smith (54)	1938	184	2 days or more	124	66.6+*
Pennoyer (43)	1938	241	5 days (average)	210	87.0
Carter, Greene and Twiss (34)	1939	316	18 hours	36	12.0
Cutler and Zollinger (7)	1940	235	—	212	90.0*
Average		1277		743	58.1
		(961)†		(707)	(73.5)

\*Approximation only.

†Excluding cases of Carter, Greene and Twiss which were observed only 18 hours.

symptoms have been reported by Taylor (30) in 5 out of 19 cases; by Kunath (31) in 1 out of 6 cases; by Graham and Hoeffle (32) in 6 out of 51 cases. Stone (33) cites a case with total gangrene 7 hours after the first pain. Graham and Hoeffle (32) found 19 cases of empyema out of 51 cases in which the patient was operated on within 48 hours after the onset. Kunath (31) encountered perforations in 2 out of 6 cases and Graham and Hoeffle (32) in 3 out of 51 cases in which the patient was operated on within 48 hours after the onset. Carter, Greene and Twiss (34) report a perforation incidence of 14.8 per cent in 81 cases in which the patient was operated on within 48 hours after the onset and list 1 case with perforation and peritonitis 2 hours after the onset.

*Clinical Course.* To gain some idea of how many of the patients may be expected to get well spontaneously

TABLE III

*Incidence of empyema of the gall bladder in acute cholecystitis*

Author	Year	Cases	Number with Empyema	Per Cent
Mentzer (16)	1932	134	43	32.0*
Zinninger (53)	1932	89	16	18.0†
Smith (55)	1933	201	18	8.9
Pratt (49)	1933	120	30	25.0
Kunath (31)	1937	90	37	41.0
Smith (54)	1938	356	—	33.3 — *
Graham and Hoeffle (32)	1938	100	30	30.0
Koster and Kasman (56)	1939	341	41	12.0
Carter, Greene and Twiss (34)	1939	574	117	20.4
Average		1423	273	19.1
(Empyema alone)				

\*Empyema, gangrene or perforation.

†Empyema with gangrene or rupture.

and how frequently the more common complications occur, an analysis of a series of reports of acute cholecystitis was undertaken. In Table II it will be seen that even excluding those patients with acute cholecystitis observed only 18 hours, no more than 75 per cent of patients will undergo spontaneous subsidence or improvement under a conservative medical regimen. It is questionable, of course, how many of the cases in the series listed in Table II were actually cases of acute cholecystitis. Undoubtedly, there must be amongst them some incorrectly diagnosed as well as an indefinite number of cases of simple biliary colic. For the most part the diagnostic criteria were sufficiently rigid to warrant the belief that these cases represent true instances of acute cholecystitis of a fair degree of severity. Empyema was found in approximately 20 per cent (Table III). Gangrene was present

TABLE IV

*Incidence of gangrene of the gall bladder in acute cholecystitis*

Author	Year	Cases	Number with Gangrene	Per Cent
Graham, H. F. (57)	1931	198	12	6.0
Judd and Phillips (58)	1933	508	68	16.4
Smith (55)	1933	201	35	17.4
Pratt (49)	1933	120	15	12.5
Taylor (30)	1936	129	29	22.5
Heuer (45)	1937	89	18	20.0
		106	23	21.0
		153	40	26.0
Kunath (31)	1937	90	24	27.0
Graham, H. F. and Hoeffle (32)	1938	100	16	16.0
Estes (5)	1938	78	34	43.4
Pennoyer (43)	1938	300	61	20.0
Glenn (59)	1939	219	59	26.9
Koster and Kasman (56)	1939	341	144	42.2
Branch (15)	1939	400	92	23.0
Carter, Greene and Twiss (34)	1939	574	219	37.9
Average		3606	889	24.6

in approximately 25 per cent (Table IV). Perforation occurred in about 10 per cent (Table V). This is a much greater incidence than the commonly quoted one of 1 to 3 per cent (35, 36, 37). The latter incidence is based upon analyses which have included both chronic and acute cases of cholecystitis, with the chronic types predominant. The same is true of generalized peritonitis which again, contrary to the commonly held opinion, is not as rare as believed. It was reported in 2.3 per cent (Table VI).

It would appear, therefore, that acute cholecystitis is not the benign condition it is usually considered. Whereas in the majority of cases the disease tends to subside spontaneously, in a goodly percentage it will not subside and many patients will develop serious complications.

*Diagnosis.* Not only is acute cholecystitis frequently accompanied by serious complications, but their

presence is often masked and their development is often insidious. Many writers have commented on the lack of correlation between the clinical manifestations and the severity of the changes in the gall bladder (16, 17, 30, 31, 34, 38, 39, 40, 41, 42, 43, 44, 45, 47). Under the term "acute cholecystitis" are grouped all grades of anatomic lesions varying from the mildest edema and congestion to advanced gangrene and perforation.

TABLE V

*Incidence of perforation of the gall bladder in acute cholecystitis*

Author	Year	Cases	Number Perforated	Per Cent
Whipple (60)	1931	160	30	19
Graham, H. F. (57)	1931	198	10	5
Mentzer (16)	1932	134	24	17.9
Judd and Phillips (58)	1933	508	61	12
Pratt (49)	1933	120	3	2.5
Branch and Zollinger (51)	1936	235	21	8.8
Taylor (50)	1936	129	15	11.6
Welton and Rothenberg (50)	1936	31	6	19.4
Heuer (44)	1936	126	13	11
Kunath (31)	1937	103	23	22
Graham, H. F. and Howe (32)	1938	100	4	4
Totten (47)	1938	100	20	20
Fates (5)	1938	78	9	11.5
Glenn (60)	1939	219	18	7.7
Graham, R. R. (14)	1939	164	11	6.7
Koster and Korman (56)	1939	341	33	9.7
Branch (15)	1939	400	8	2
Carter, Greene and Twiss (34)	1939	574	69	12
Average		3720	378	10.1

There are no criteria which will serve reliably to distinguish the various changes. It is impossible in any one patient, to say whether the clinical course will be remissive or progressive, and it is impossible before operation to determine the exact nature and extent of the inflammatory lesion.

Tourolff (42) concluded that some 20 per cent of patients with acute cholecystitis who have few if any clinical manifestations will show at operation gangrene or large sized pericholecystic abscesses. Totten (47) found that about 14 per cent of his patients had serious lesions at operation, although clinically the trouble appeared to be subsiding. In Kunath's series (31), of 32 patients who had recovered clinically with some delay, 12 had empyema and 6 had a pericholecystic abscess. Mentzer (16) described 4 perforations occurring in 63 patients under medical observation, none of which were recognized. Behrend and Gray (39), reporting on 200 consecutive cases of acute cholecystitis seen at the Mayo Clinic, found discrepancies between the clinical and pathologic findings in 50 per cent. Pennoyer (43) at the Roosevelt Hospital in New York, found that only about half of the cases diagnosed as acute by the pathologist were clinically acute. Kunath (31) noted that in 103 proven cases of

acute cholecystitis, 13 of the patients did not present acute symptoms at the time of admission.

### TYPES OF MANAGEMENT ADVOCATED

**Radical.** The inability to forecast the clinical course in a given patient and the inability in many instances to recognize the presence of serious changes are the chief reasons why the so-called "radicals" propose an immediate or early operation for every patient with acute cholecystitis. It is the contention of this group that the risk of operation in the acute stage is less than the risk of the development of fatal complications. They stress the high mortality in complicated cases and argue that early removal of the gall bladder will alone prevent these. Contrary to the claims of their conservative opponents, many patients, they point out, will not get well spontaneously nor will the obstruction relieve itself under medical management. They contend that the inflammation and edema actually make the removal of the gall bladder from its bed easier. They emphasize that postoperative complications are fewer and hospital stays shorter in those patients subjected to early operation.

**Conservative.** Because in the majority of patients the disease will quiet down, the conservatives advocate laissez-faire medical treatment during the acute stage and operation later. This group has emphasized the fact that the mortality rate of operations performed during the acute stage is much greater than that of the delayed operations. They point out that great skill

TABLE VI

*Incidence of generalized peritonitis in acute cholecystitis*

Author	Year	Cases	Number with Generalized Peritonitis	Per Cent
Judd and Phillips (58)	1933	508	3	0.59
Pratt (49)	1933	120	1	0.83
Graham, R. R. (61)	1935	153	2	1.47
Taylor (50)	1936	129	4	3.1
Branch and Zollinger (51)	1936	235	6	2.55
Heuer (44)	1936	126	1	0.79
Kunath (31)	1937	103	4	3.9
Fates (5)	1938	78	2	2.6
Smith (54)	1938	377	4	1.1
Totten (47)	1938	100	1	1.0
Graham, R. R. (14)	1939	273	3	1.1
Koster and Korman (56)	1939	341	9	2.6
Carter, Greene and Twiss (34)	1939	574	32	5.6
Average		3096	72	2.3

and judgment are required when operating in an infected area where oozing is great and structures are easily torn. Moreover, the inflammation and swelling during the acute phase obscures anatomical landmarks and in many instances prevents cholecystectomy or exploration of the common duct. Many patients, therefore, will have to have a subsequent operation with its added risk.

TABLE VII

*The mortality after "early" operation for acute cholecystitis*

Author	Year	Cases	Deaths	Per Cent
Love (52)	1929	38	8	21.0
Zininger (53)	1932	35	3	8.5
Pratt (49)	1933	45	10	22.2
Judd and Phillips (55)	1933	14	1	7.1
Lipshutz (4)	1935	20	0	0.0
Graham, R. R. (61)	1935	6	1	16.6
Branch and Zollinger (51)	1936	34	7	20.5
Heuer (45)	1937	153	5	3.2
Kunath (31)	1937	41	3	7.3
Graham, H. F. and Hoefle (32)	1938	100	9	9.0
Pennoyer (43)	1938	59	15	25.0
Smith (54)	1938	127	16	13.0
Totten (47)	1938	(100)	..	10.2
Finsterer (12)	1939	62	4	3.2
Koster and Kasman (56)	1939	341	32	9.38
Glenn (59)	1939	219	70	31.9
Graham, R. R. (14)	1939	19 (ward) 6 (pvt.)	3 1	15.7 16.4
Carter, Greene and Twiss (34)	1939	425	98	23.0
Average		1744	286	16.4

*Analysis of results.* In order to gain some appreciation of the actual results being obtained by the proponents of both of these schools, an analysis was made of the mortality in a series of cases reported from leading clinics.

It is impossible to compare accurately groups of cases of "acute cholecystitis" reported by different observers from different clinics. The mortality in any one series is affected by the proportions of mild, severe and complicated cases. Diagnostic criteria vary and the report on the nature of the lesion is based often on mere surgical inspection. To a considerable extent these sources of error have been avoided in the present

TABLE VIII

*The mortality resulting from conservative treatment for acute cholecystitis*

Author	Year	Cases	Deaths	Per Cent
Judd and Phillips (58)	1933	508	24	4.7
Graham, R. R. (61)	1935	153 (ward) 52 (pvt.)	10 4	6.5* 7.7*
Branch and Zollinger (51)	1936	235	24	10.2
Walters (2)	1937	76	3	3.9
Bergh (10)	1938	435	8	1.8
Pennoyer (43)	1938	300	30	10.0
Doran (62)	1939	30	1	3.3
Graham, R. R. (14)	1939	273 (ward) 68 (pvt.)	16 2	5.8* 2.5*
Walters, Gray and Priestley (18)	1939	73	3	4.1
Average		2203	125	5.6

\*Includes deaths in group refusing operation.

analysis. The majority of the reporters of the series of cases selected for comparison have based their diagnosis on pathologic findings. Where clinical findings alone have been used as the criteria for diagnosis, the standards have been rigid enough to warrant the belief that only true cases of a fair degree of severity are represented.

In Table VII there is listed a series of cases in all of which the patient was operated on "early." In Table VIII there is given the total mortality in various series in which the patients were treated for the most part conservatively. The mortality figures in this group include the deaths in those patients subjected to early as well as late operation, and, in some instances, the deaths as well in patients not coming to operation at any time. A comparison between these results shows a mortality rate three times as great in those patients operated on "early" as in those treated conservatively.

Throughout the literature on the management of acute cholecystitis the terms "early," "late," "immediate" and "delayed" occur frequently. Yet, there is lacking a uniform definition of what these terms mean. "Early" operation may mean within thirty-six hours,

TABLE IX

*The mortality after operations for acute cholecystitis*

Author	Year	"Immediate" Operation			"Delayed" Operation		
		Cases	Deaths	Mort. %	Cases	Deaths	Mort. %
Love (52)	1929	38	8	21.0	69	7	10.1
Zininger (53)	1932	35	3	8.5	54	4	7.4
Graham, R. R. (61)	1935	6	1	16.4	62	3	4.8
Branch and Zollinger (51)	1936	34	7	20.5	195	17	8.7
Graham, R. R. (14)	1939	19	3	15.7 (wd.)	164	7	4.2
		6	1	16.4 (pvt.)	57	1	1.75
Average		138	23	16.6	601	39	6.4

Author	Year	"Early" Operations		"Late" Operations	
		Cases	Mortality %	Cases	Mortality %
Finsterer (12)	1939	62	3.2	97	7.2

within five days, or even later than five days. "Delayed" operation means after from twenty-four to forty-eight hours, or after weeks or even months. "Late" operation means after from two to four days or longer. It may mean months after the onset. Equal confusion exists as to whether the time interval has been measured from the onset of the illness or from the time when the patient was first seen. Because of this confusion there must be some degree of overlap and duplication of material in the various reports.

It is apparent from Table IX that the mortality rate is about two and a half times as great with "immediate" as with "delayed" operation. The sole exception is found in the statistics of Finsterer (12).

When comparison is made in those cases in which the actual period elapsing between the time when the patient was seen and when he was operated on is given, it is again apparent that the mortality is far greater in those cases in which the patient was operated on after the lapse of only six, twelve, or twenty-four hours (Table X).

The one trend favoring the views of the radical proponents is seen in Table XI. When the mortality is correlated with the duration of the acute symptoms it is found to be much lower in the cases in which operation was performed within forty-eight hours after the onset. It was only a fourth that of operations carried out more than forty-eight hours after the onset of symptoms.

*Comment.* Despite the favorable mortality rate of operations done within forty-eight hours of the onset of the acute symptoms, there are objections to the routine application of so early an operation. Pennoyer (43) found that the disease was incorrectly diagnosed in 32 out of 59 patients (54 per cent) operated on within twelve hours after admission. Graham (14) at Toronto likewise reported nine errors in diagnosis in 19 cases (48 per cent) in which the patient was oper-

ated on immediately. Obviously then, if every patient with the clinical diagnosis of acute cholecystitis were to be operated on as soon as the diagnosis was made, a number would have a major surgical operation when they didn't have the expected disease.

Another objection to routine prompt operation is that in some patients the edema and swelling present in the early acute phase of cholecystitis will prevent anything more than a cholecystostomy being done. The same changes will also prevent adequate exploration of the common duct. As seen in Table XII practically 1 out of every 10 patients with acute cholecystitis harbors stones in the common duct, and as more ducts are explored it is likely that this percentage will be found to increase. In such instances, then, secondary operations will be necessary and the mortality of these will have to be added to that of the first operation.

Actually, it is uncommon in hospital practice to see a patient within the first hours of his or her acute attack. The average patient has been ill from three to four days before admission.

Furthermore, no two patients present the same problem when first seen in an acute attack. Their past history of gall bladder disease is of varying duration and their "present attack" is likewise of varying duration. The severity of the current attack differs and the degree and number of complications attendant are diverse. Age varies widely. Jaundice may or may not be present. Diabetes mellitus, cardiovascular disease and obesity, those common concomitants of gall bladder disease, may be present in some and absent in others. Dehydration and electrolyte imbalance is seen in one, and chemical normalcy in the other. All of these varying factors exert an influence on the mortality and it may be impossible to evaluate them by any short examination.

Acute cholecystitis, then, can have no uniform

TABLE X

*The mortality after operations for acute cholecystitis correlated with the duration of pre-operative observation*

Author	Year	Within 6 Hours After Admission			More Than 6 Hours After Admission		
		Cases	Deaths	Mort. %	Cases	Deaths	Mort. %
Carter, Greene and Twiss (34)	1939	128	20	15.6	446	44	9.8

Author	Year	Within 12 Hours After Admission			More Than 12 Hours After Admission		
		Cases	Deaths	Mort. %	Cases	Deaths	Mort. %
Graham, R. R. (61)	1935	6	1	16.0	62	3	4.8
Pennoyer (43)	1938	59	15	25.0	241	12	5.0
Graham, R. R. (14)	1939	19	3	15.7 (wd.)	164	7	4.2
		6	1	16.4 (pvt.)	57	1	1.75
Average		90	20	22.2	524	23	4.4

Author	Year	Within 24 Hours After Admission			More Than 24 Hours After Admission		
		Cases	Deaths	Mort. %	Cases	Deaths	Mort. %
Mentzer (16)	1932	21	8	38.0	21	2	9.5
Kunath (31)	1937	41	3	7.3	49	2	4.0
Totten (47)	1938	(100)		10.2	(100)		13.5
Smith (54)	1938	127	16	13.0	229	14	6.0
Average		189	27	14.2	299	18	6.0

method of treatment, determined by one simple rule. The treatment must be individualized.

### REGIMEN EMPLOYED

Because of the danger of complications, the difficulty in recognizing them, and the need to evaluate all physiological abnormalities which might be present, immediate hospitalization of every patient is recommended.

Those patients with signs of perforation and peritonitis or with fever, rapid pulse, marked leukocytosis and a large, tender gall bladder suggesting imminent perforation should usually be operated on promptly. If jaundice is present, it is usually well to postpone operation until the bilirubinemia has become stabilized, but this should be done only if the condition of the patient warrants some delay in operating. In such cases one must usually be content with a cholecystostomy.

After the temperature has returned to normal and convalescence is well under way, delayed cholangiography may be done to determine the presence of calculi and the size and patency of the common duct. After adequate preparation then with glucose, Vitamin K and bile salts, a secondary cholecystectomy with or without choledochostomy is done. As a rule this is done before the patient is permitted to leave the hospital, but in some instances the patient is allowed to return home for an interval with the drainage tube in situ. In rare cases because of advanced age, severe cardiovascular disease or other changes rendering the patient a bad risk, no other operation is done.

Whenever the condition of the patient when first seen permits, and it does in the majority of instances, an initial conservative regimen is instituted. The patient is placed at rest. Pain is alleviated. Food by mouth is withheld during the first twenty-four hours or until nausea and vomiting have abated, and fluid and glucose are given parenterally. If abdominal distention is present, continuous suction by means of a Wangenstein apparatus is maintained. A white blood cell count and a differential count are done when the patient is admitted and these are repeated at intervals.

A Van den Bergh test is done at the outset and is repeated if the initial reading showed a hyperbilirubinemia or if clinical jaundice appears. A scout film of the abdomen may be taken, but if this requires disturbing the patient too much it is dispensed with. The making of other blood studies for the determination of electrolyte balance is dependent on the condition of the patient. If there has been much vomiting and loss of fluids and the patient appears dehydrated and probably hypochloremic and azotemic it is necessary to determine the blood chlorides, urea nitrogen and carbon dioxide combining power. If the patient is a diabetic or has renal disease, frequent determinations of the blood sugar and blood urea nitrogen are, of course, necessary.

If, during the first twenty-four or thirty-six hours, the temperature and pulse continue to mount; if the local signs of disease increase and white blood counts show a progressive elevation in total cells and neutrophil percentage with possibly a shift to the left, operation is no longer delayed. If, after from thirty-six to forty-eight hours, the temperature has not dropped, if the pulse remains rapid, if the abdominal signs have grown more alarming, if the white blood cell count is still elevated and possibly a little higher than on admission, and if the general appearance of the patient is not improving, operation again is no longer delayed.

If, during the first twenty-four or thirty-six hours, the temperature, pulse rate and leukocyte count begin to decline, the abdominal signs begin to regress or even if they remain stationary, and if the general condition begins to show evidence of improvement, a conservative attitude is maintained.

After all the signs of inflammation have subsided, and not until then, diagnostic studies are undertaken. These consist of a cholecystogram, biliary drainage, several tests of liver function, prothrombin estimation, perhaps blood typing and occasionally some tests of renal function. Following these if it is decided to operate on the patient, he or she is prepared in the usual manner, with glucose, Vitamin K, bile salts and vitamin concentrates.

TABLE XI

*The mortality after operations for acute cholecystitis correlated with the duration of the acute symptoms*

Author	Year	Operation Within 48 Hours of Onset			Operation After 48 Hours of Onset		
		Cases	Deaths	Mort. %	Cases	Deaths	Mort. %
Graham H. F. (57)	1931	20	1	5.0	178	11	6.2
Zinninzer (53)	1932	12	0	0	23	3	13.0
McKenty (63)	1935	14	0	0	..	..	..
Taylor (30)	1936	19	1	5.2	83	16	19.2
Wilson, Lehman and Goodwin (64)	1936	11	0	0	..	..	..
Heuer (44) (45)	1937 1937	50	2	4.0	..	..	..
Kunath (31)	1937	6	0	0	..	..	..
Tetten (47)	1938	26	0	0*	..	..	..
Graham, H. F. and Hoeft (32)	1938	51	2	3.92	49	7	14.2
Stone (23)	1938	2	0	0	..	..	..
Walters (65)	1938	7	0	0	..	..	..
Average		218	6	2.7	333	37	11.1

\*Within 72 hours of onset.

TABLE XII  
Incidence of common duct stones in cases of acute cholecystitis

Author	Year	Cases	Number With Stones	% Stones	Number of Ducts Explored	% of Explored Ducts Containing Stones
Branch and Zollinger (51)	1936	229	19	8.3	45	42.2
Kunath (31)	1937	90	6	7		
Glenn (59)	1939	219	9	4.1	22	40.9
Graham, R. R. (14)	1939	57	6	10.5		
Koster and Kasman (56)	1939	341	24	7	341	7 (7)
Carter, Greene and Twiss (34)	1939	574	80	14	98	81.6
Walters and Snell (17)	1940	508	43	8.5		
Cutler and Zollinger (7)	1940	115	19	16.5	37	51.4
Average		2133	206	9.6	543	27.8 (62.8)*

\*Excluding cases of Koster and Kasman as it is not too clear if the common duct in every one of their cases was actually explored.

## SUMMARY AND CONCLUSIONS

1. Acute cholecystitis is usually dependent on an obstruction to the outlet of the gall bladder with interruption in the blood supply to the organ. In over 92 per cent of cases the obstructing agent is a calculus. Secondary infection of the ischemic areas may or may not occur.

2. Acute cholecystitis is a dangerous condition. Under conservative treatment perhaps 25 per cent of the patients will get worse. Serious complications such as empyema, gangrene, perforation of the gall bladder and generalized peritonitis frequently occur.

3. Unfortunately in these cases there is no good correlation between the severity of the clinical manifestations and the severity of the disease. Furthermore, it is impossible to predict in any one case whether the disease will quiet down or get worse.

4. Statistics show that the mortality is great in the "early" operations done after the symptoms have been present for forty-eight hours. Operations done within forty-eight hours after the onset of the acute attack have had the lowest mortality rate. Unfortunately few patients reach a hospital within this interval.

5. It is inadvisable, however, to operate on every patient seen within forty-eight hours after the onset of acute symptoms. If such an early operation is done as a routine many diagnoses will be wrong and patients will be operated on unnecessarily.

6. Patients and the disease vary widely, and hence the treatment must be individualized.

7. A plan of procedure which has been employed successfully in the management of patients with acute cholecystitis is outlined.

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Color Photography Through the Sigmoidoscope\*

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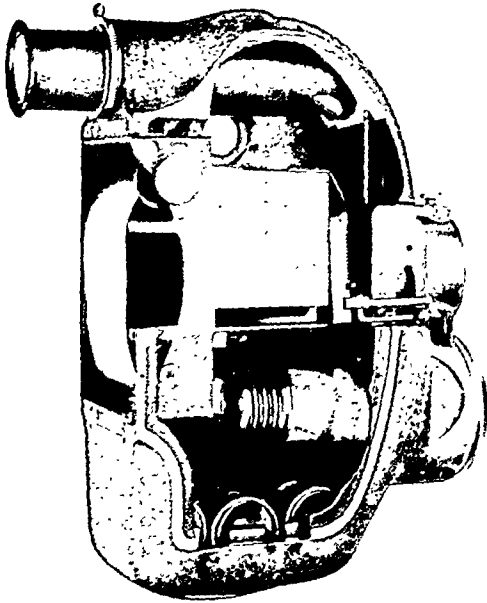
A PHOTOGRAPHIC instrument has been designed which now makes it possible, as a simple practical procedure, to photograph in full color the bowel wall as far up as it can be visualized through the sigmoidoscope.

The principle upon which this special camera works is simple. The source of light for photographing purposes is a small photo-flash bulb. A series of mirrors and prisms directs the light into the sigmoidoscope, and it furnishes adequate illumination for photographing a film in color. An electrical mechanism synchronizes the flash with the shutter, and a single exposure is made with each flash. A view finder and a pilot light make possible the visualization of the bowel wall through the sigmoidoscope. Sigmoidoscopic tubes of suitable lengths for the different lenses attach the instrument to the sigmoidoscope, thus ensuring accurate focusing of the section to be photographed. This section is focused in the view finder, a process that is simple and gives accurate results. When the focusing is completed, a release wire is pushed. The flash of the bulb and the action of the shutter are electrically synchronized, and with the release of the wire, these come into action and the picture is taken.

The importance of this device lies in the fact that it is now possible to record in full color the findings of sigmoidoscopic examination. Thus it is possible to study more carefully and more accurately the course of the disease present in the bowel. This is of particular importance in cases of chronic ulcerative colitis, because it makes possible an objective record of the bowel wall which eliminates the personal element in the evaluation of this type of case. In addition, the physician can now make a careful study of the films at his leisure and can gain valuable information which hitherto has been rendered difficult to obtain because of the impossibility of keeping the patient in position

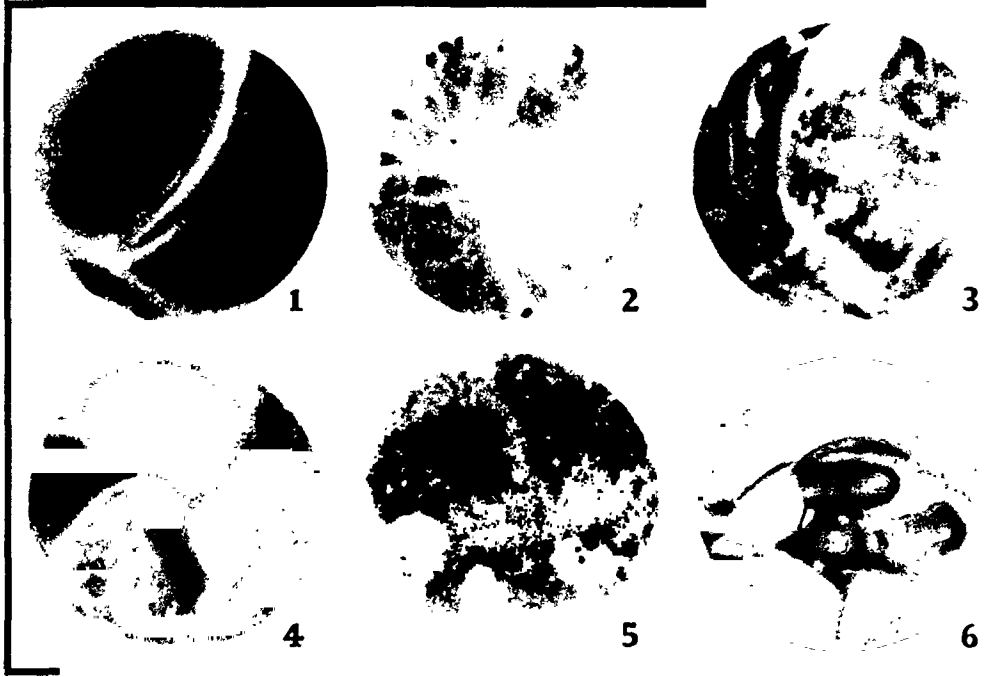
long enough to make a detailed study of the field under observation.

This instrument has been designed and manufactured by the Cameron Surgical Specialty Company, and once the initial cost of purchasing it has been met, the cost of upkeep is very little. Each photograph calls



for the use of a photo-flash bulb, which costs about ten cents, depending upon the type of bulb used, and a film, which costs about eleven cents, making a total cost of twenty-one cents. The films used are standard black and white, Kodachrome, or Dufay process color films. The purchase price of the films covers the processing, so that no additional expenditure is entailed.

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1. Normal bowel—recto-sigmoid fold.
2. Stricture of rectum following chronic ulcerative colitis. Note hemorrhages from edematous friable mucosa following attempts to enter stricture with sigmoidoscope.
3. Chronic ulcerative colitis with streaks of mucus still adherent.
4. Polyp of the sigmoid as seen from just below the recto sigmoid fold.
5. Single ulcers of the rectum—traumatic due to patient's finger nail. Note the moderate degree of atrophy of mucosa with capillaries showing through the thin membrane.
6. Multiple polyposis in a patient with lymphogranuloma venerum with positive Frei test.





# The Effect of Various Bile Acids on the Volume and Certain Constituents of Bile\*

By

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**PURPOSE OF THIS INVESTIGATION:** This investigation was undertaken chiefly for three reasons: (1) to study the choleretic effect of different bile acids with the idea of ascertaining the relation of structure to choleresis, (2) to determine the effect of different bile acids on the composition of bile, and (3) to determine, if possible, how the body metabolizes the oxidized bile acids. These purposes have only in part been achieved, because the problem is complex and chemical methods are limited.

hydroxyl (OH) groups attached to the cholane nucleus (Fig. 1). The most common bile acid is *cholic acid*, or 3,7,12 *tri*-hydroxycholanic acid. This bile acid is present in human bile in relatively large amounts. Human bile also contains *desoxycholic acid*, or 3,12 *di*-hydroxycholanic acid. The third bile acid in human bile is *lithocholic acid*, or 3, mono-hydroxycholanic acid. A fourth is 3,7 *di*-hydroxycholanic acid or cheno-desoxycholic acid. It is to be noted that these four bile acids differ only in regard to the number of OH

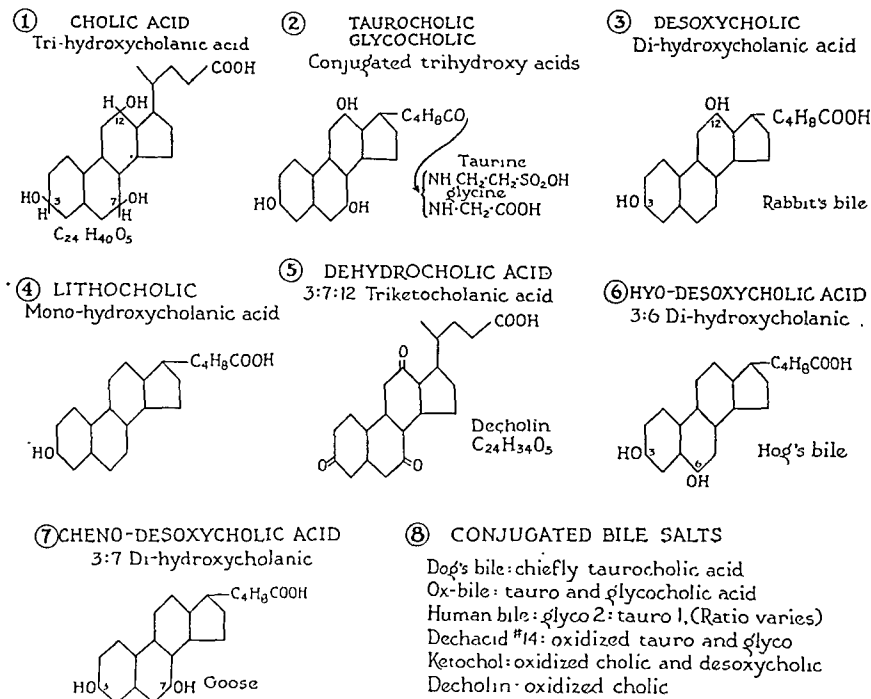


Fig. 1

**Bile Acids:** The bile acids have as their basic structure the cholane nucleus which consists of the cyclo-pentenophenanthrene ring. They are rather closely related to cholesterol, the sex hormones, the glucosides, the carcinogenic hydrocarbons and Vitamin D. The difference between the various natural bile acids depends upon the number and the position of the

groups; this is shown in Fig. 1. These bile acids are present in bile chiefly in the conjugated form, i.e. in combination with taurine and glycine. Since the conjugated forms of cholic acid predominate in human bile, it is frequently taught or implied that human bile contains only the sodium salts of glycocholic and taurocholic acids. However, the conjugated forms of desoxycholic acid and lithocholic acid are also present, as is cheno-desoxycholic acid and all the bile acids in human bile are not conjugated. This latter bile acid is

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characteristic of the bile of the goose. Desoxycholic is more characteristic of rabbit's bile. Hog's bile is characterized by hyo-desoxycholic acid, or 3-6 dihydroxycholic acid, which is interesting in that one of the OH groups is attached to the sixth carbon rather than the seventh. It is also worthy of note that Sobotka (18) reports that 3-hydroxy-12 ketocholic acid, a partially oxidized bile acid, is present in human bile. So, oxidized bile acids are apparently not foreign to human bile.

When the various bile acids are oxidized, the OH groups are converted to  $C=O$  groups, which are referred to as carbonyl or ketone groups. The resulting bile acid is referred to as a keto-acid or a dehydro-acid. Referring to Fig. 1, it will be noted that "Decholin" (Riedel-de Haen) is oxidized cholic acid and is known chemically as dehydrocholic acid, or 3,7,12 triketocholic acid. ("Procholon," Squibb, is also dehydrocholic acid). It is to be noted further that it is not conjugated with taurine or glycine. Hence, it is an oxidized unconjugated bile acid. "Ketochol" (Searle) and "Kebilac" (Wilson Laboratories) contain oxidized unconjugated cholic, desoxycholic and lithocholic acids, chiefly the former; or they are composed of a mixture of ketocholic acids. That is, the taurine and glycine are split-off from Ox-bile salts and the remaining bile acids are oxidized. It is possible to oxidize the conjugated bile acids of Ox-bile without splitting-off the glycine and taurine. Such a bile acid is referred to as an oxidized conjugated bile acid. We have used such a bile acid which is called commercially "Dechacid No. 14" (Wilson Laboratories) and is chiefly oxidized taurocholic and glycocholic acids, although it probably contains some oxidized conjugated desoxycholic and lithocholic acids.

As a source of unoxidized conjugated bile acid, we have used "Bilron" (Lilly), which contains approxi-

mately 50 per cent of cholic acid, and "Ox-bile Salts" (Wilson Laboratories), which contains approximately 57 per cent cholic acid. As a source of oxidized conjugated bile acids, we have used "Dechacid No. 14," which by analysis for keto groups yields 11.2 per cent of keto ( $C=O$ ) groups, or expressed as triketocholic acid, 53.6 per cent triketocholic acid. All the bile acids in this preparation are probably oxidized, the low value for keto groups being due to its glycine and taurine content and the presence of di- and mono-ketocholic acids. As a source of pure oxidized unconjugated cholic acid, or triketocholic acid, we have used "Decholin" (Riedel-de Haen), which by the analysis for keto groups is practically pure triketocholic acid and contains 20.9 per cent keto groups. As a source of oxidized unconjugated bile acids we have used "Ketochol" (Searle), which by the analysis for keto groups yields 18.3 per cent keto groups, or expressed as triketocholic acid, 87.6 per cent triketocholic acid. We have also used "Kebilac" (Wilson Laboratories) which contains oxidized unconjugated bile acids and is analogous to "Ketochol." This latter product yields 18.6 per cent keto groups, or expressed as triketocholic acid, 89.9 per cent triketocholic acid. The values for "Ketochol" and "Kebilac" are not 100 per cent, as in the case of pure triketocholic acid (Decholin), because these products contain di- and mono-ketocholic acids. It should be added that we did not use "Ketochol" as dispensed in tablets because of the presence of an excipient or binder.

In this work the doses of the various bile acids were accurately weighed and the capsules used were accurately filled. In addition every preparation used was assayed for cholic acid and for keto groups. This is emphasized because this was not done in previous work (8) and it is essential for the comparative studies made in this paper. The point is that in this

TABLE I

Protocol illustrating the usual plan of an experiment to determine the recovery of cholic acid fed and the effect of cholic acid as natural ox-bile salts on the excretion of keto-reacting substances

Dog	Regime	Volume cc./24 Hrs.	Cholic Acid Mgs./24 Hrs.	Cholesterol Mgs./24 Hrs.	Pigment Mgs./24 Hrs.	*Keto Acids Mgs./24 Hrs.	Total Solids Mgs./cc.
No bile or bile salts returned to the intestine							
3	Control						
14.5 K	1st day	151	2159**	34.0	108.1	322	49
	2nd day	140	1904	21.0	108.2	328	46
	3rd day	145	1914	31.0	108.7	302	46
	Average	144	1992	32.0	105.3	317	47
3 Gms. Ox-bile salts containing 1.71 gms. of cholic acid							
	1st day	198	2584	40.6	103.1	453	53
	2nd day	176	3613	37.0	99.7	375	56
	3rd day	179	3276	32.7	98.9	267	49
	Average	185	3458	36.8	100.6	365	53
	Control						
	1st day	155	1891	20.0	83.1	507	41
	2nd day	144	1699	21.9	116.1		
	3rd day	160	1840	25.3	139.5		
	Average	153	1877	22.4	112.6		

\*Keto-reacting substances calculated as triketocholic acid.

\*\*The basal cholic acid output was unusually high in this animal, since most of the values range from 1.2 to 1.6 grams with an average of 1.38 gm. per day. The control cholesterol output is also unusually high.

TABLE II

*Showing the accuracy of the method for the determination of carbonyl or keto groups in bile*

	Mgs. keto-reacting-substances per 100 cc. of bile										
	267	219	559	594	348	255	186	516	395	152	150
Sample 1	267	219	559	594	348	255	186	516	395	152	150
Sample 2	201	258	516	556	326	267	176	517	405	145	167

\*Samples 1 and 2 represent random duplicate analyses of the same bile. The eleven biles, the duplicate analyses of which are illustrated, were obtained under different conditions. The maximum spread between duplicate analyses on the same bile was usually not more than 12.5 mg. per cent.

work we have made a serious attempt to obtain quantitative results on the various bile acids, as quantitative as the chemical methods available and the bile fistula method permit at this time.

### METHODS

The biliary fistula dogs (Rous-McMaster Method) were maintained on a standard diet of 230 grams of "Pard" and 200 cc. of milk, consisting of 9 per cent carbohydrates, 12 per cent proteins, and 6 per cent fat; these amounts were fed twice a day. The animals were first placed on a "control period," during which they were maintained on the standard diet for 3-4 days without the oral administration of any bile salts. The bile produced by the animal was not returned. At the end of each 24 hours the bile secreted was collected and an aliquot was removed for chemical analysis. Volume output, cholic acid, cholesterol and pigment outputs, and specific gravity were determined each day. The viscosity was also determined. At the end of this "control period" an adequate aliquot of the total volume was removed for the analysis of carbonyl

### *Recovery of carbonyl groups added to normal dog bile*

	Mgs. Keto Groups Added	Mgs. Keto Groups Recovered	% Recovery
Sample No. 1	41.76	40.9	97.9
Sample No. 2	94.7	94.1	99.3

groups and for the determination of total solids. In many instances carbonyl and total solid analyses were made each day. Thus, the basal outputs of the various bile constituents were obtained. During the next 3-5 successive days the bile salt to be tested was administered in divided doses after meals. As in the control period, the bile constituents were determined each day, and at the end of the "test period" a portion of the total volume was removed for carbonyl analysis and total solid determination. The average values for the "test period" were then compared with the "control period." The data in Table I illustrate the method used for analyzing the effect of a bile salt on the volume and constituents of bile. This means that a minimum of three months is required to make ten tests on any particular bile preparation, since we believe that a minimum of ten tests on at least five dogs is required to yield average values of comparative worth. The animal and last results are discarded on the first evidence of the development of a hepatitis, shown by a decrease in cholic acid synthesis on the basal diet.

Three and five gram doses per day of the various preparations were used. Larger doses of bile salts

were not used because seven grams sometimes provoke diarrhea and the daily output of bile in most dogs when it is circulated through the entero-hepatic circuit three times daily is usually not greater than about six grams.

Bile acids were determined as cholates by Reinhold and Wilson's modification of the Gregory-Pascoe method (2). Cholesterol was determined by the method of Elman and Taussig (3). Total pigment was determined according to the method of Schmidt and Jones (4). Specific gravity was determined with the aid of the hydrometer at the room temperature of 25° C. Total solids were determined by drying the bile at 110° C. and 25 mm. pressure. The carbonyl groups were determined by a method devised, by Dr. Gustus of the Wilson Laboratories (5). The principle of this method is as follows: The carbonyl groups in the bile are allowed to react with an excess of hydroxylamine. The remaining hydroxylamine is combined with diacetyl-monoxime converting the latter to the dioxime compound. The dioxime is precipitated with nickel acetate, and the resulting precipitate washed, dried and weighed. By calculations, the weight of the carbonyl groups that combined with the hydroxylamine can be obtained. The data in Table II illustrate the accuracy of Dr. Gustus' method which will be published elsewhere. The identity and source of the various samples were unknown to Dr. Gustus. When pure triketocholanic acid is added to bile from 95 to 99 per cent is recovered. The method is tedious and requires the full time of a chemist for one week to make eight determinations.

### RESULTS

*Are keto-reacting substances normally present in dog's bile?* This question had to be answered in order to ascertain to what extent the oxidized or keto acids administered orally were absorbed and excreted in the bile. So in all instances before an oxidized bile acid was administered, the control output of keto-reacting substances in the animal's bile was determined. This was done in 15 dogs receiving the control diet and no bile salts. The control daily output of keto-reacting substances expressed as triketocholanic acid ranged from 98 to 507 milligrams per 24 hours. The average value for all the tests was  $252 \pm 16$  (S.E. of mean).

*Effect of the various bile acids on volume output.* The results are shown in Table III. I. A significant difference between the two "natural Ox-bile salt" preparations does not exist. However the Ox-bile salts (Wilson) manifest a trend toward producing a greater cholesteris than Bilon, which is readily explained by the slightly greater cholic acid content of the former. Neither contains appreciable amounts of desoxycholic acid, which is not, according to our preliminary studies, as good a choleric as pure cholic acid. II.

The oxidized conjugated Ox-bile salts in Dechacid had a no greater choleric effect than the natural unoxidized conjugated bile salts. An inspection of Table VIII, however, shows that the choleresis was characterized by only a very slight decrease in concentration of bile acids. III. The oxidized unconjugated bile acids, Decholin, Ketochol and Kebilac were per gram weight the most potent choleric. For example, 2.85 grams of cholic acid, as it exists in 5 grams of Ox-bile salts (Wilson), that is, unoxidized and conjugated, produced an average increase in bile volume of 67 per cent, whereas 3 grams of oxidized cholic acid, as Decholin, caused a 106 per cent increase. This difference is statistically very significant since no overlapping occurred in the data (per cent increase) obtained with the two preparations.

*Comment.* The foregoing results have a bearing on the question: What portion of the cholane nucleus (and related compounds) is responsible for choleresis? Since Dechacid No. 14 is oxidized but conjugated, and its related product, Ketochol, is oxidized but not conjugated, it would appear that conjugation suppresses choleric action. Three and 5 grams of Dechacid, which contained as much cholane nucleus as the same amounts of natural bile salts, caused approximately the same increase in volume output of bile as 3 and 5 grams of the "natural cholates" (Table III). If conjugation had not suppressed the choleric action of the keto groups in Dechacid, then the 3 grams of Dechacid should have produced a 60 per cent increase instead of only a 39 per cent increase. This statement is based on the following calculation: 3 gm. of Ketochol (18.3 per cent keto groups) cause a 99 per cent increase in

the volume output of bile. Assuming the increase to be proportional to the content of keto acid, Dechacid (11.2 per cent keto groups) would have produced  $99 \times 11.2/18.3 = 60$  per cent increase. It should be pointed out, however, that the suppression of the choleric action of the oxidized cholic acids by conjugation may not be true of all bile acids. It may depend on the position and the number of the keto groups in the cholane nucleus. It should also be pointed out that Dechacid contains a number of bile acids. Before one can finally conclude that conjugation suppresses the choleric activity of an oxidized bile acid, it will be necessary to use the individual bile acids. For example, the choleric activity of pure cholic, pure taurocholic, pure glycocholic and pure oxidized glycocholic acid will have to be studied.

*Effect of various bile acids on cholic acid output.* I. The administration of the "natural Ox-bile salts" increased the cholic acid output in the bile. The output was increased above the basal control output, approximately 90 per cent when 3 grams of the Ox-bile salt preparations were given, and approximately 156 per cent, when 5 gms. were given. II. The oxidized conjugated bile salts given as Dechacid No. 14 had no significant effect on cholic acid output (Column B, Table III). III. The oxidized unconjugated bile acids did not, when all the results are averaged, have a significant effect on cholic acid output. However, when 5 grams were administered, the cholic acid output fluctuated considerably, or more than we have observed to date with the natural bile salts and with Dechacid No. 14. With 5 gms. of Decholin, for example, in one case the output of cholic acid was decreased 34 per cent and in

TABLE III

Showing the effect of various bile acids on the volume output and certain constituents of bile

BILE ACID	No. of Doses	Total Tests	A. Volume cc. per 24 hr.			B. Cholic Acid Output Mgm. per 24 hr.			C. Total Cholic** Acid Recovered Mgm.			D. Cholesterol Output Mgm. per 24 hr.			E. Pigment Output Mgm. per 24 hr.			F. Total Solids Mgm. per cc.			G. Specific Gravity, 25° C.	
			C	T	% Change	C	T	% Change	C	T	% Recov.	C	T	% Change	C	T	% Change	C	T	% Change	C	T
3 GM. BILRON 1.5 GMS. CHOLIC ACID (FE OX BILE SALTS)	13	28	126	166	+ 31	1422	2744	+ 92	2922	2744	- 6	10	18	+80	100	104	+ 4					
5 GM. BILRON (FE OX BILE SALTS) 2.5 GMS. CHOLIC ACID	9	11	128	197	+ 54	1292	3313	+156	3782	3313	-12	9	17	+80	107	110	+ 2					
3 GMS. OX BILE SALTS 1.71 GMS. CHOLIC ACID	8	15	133	162	+ 36	1493	2509	+ 88	3203	2509	-12	12	16	+33	115	105	- 8	36	44	+22	1010	1011
5 GMS. OX BILE SALTS 2.5 GMS. CHOLIC ACID	6	15	127	212	+ 67	1407	3619	+157	4257	3619	-12	10	17	+70	102	108	+15	37	50	+35	1011	1013
3 GMS. No. 14 DECHACID. (CONJUGATED OXIDIZED OX BILE SALTS)	11	14	125	175	+ 39	1435	1559	+ 8	3000	455	16	11	15	+36	104	100	- 4	39	40	+ 2	1011	1011
5 GMS. No. 14 DECHACID	8	10	131	200	+ 53	1403	1477	+ 6	5000	700	14	11	12	+ 9	125	108	- 8	37	38	+ 2	1011	1011
3 GMS. KETOCHOL (MIXTURE) OF KETOCHOLANIC ACIDS	7	10	126	251	+ 99	1468	1565	+ 6	3009	725	24	11	14	+27	114	105	- 7	35	32	- 8	1012	1010
5 GMS. KETOCHOL	8	10	121	273	+125	1383	1445	+ 4	5000	1145	23	10	14	+40	109	136	+25	36	32	-11	1011	1010
3 GMS. DECHOLIN (DEHYDROCHOLIC ACID)	6	10	125	264	+106	1473	1647	+ 12	3000	835	28	11	8	-27	114	129	+13	35	30	-22	1011	1010
5 GMS. DECHOLIN	6	10	119	291	+144	1354	1340	- 1	5000	1213	24	9	4	-55	124	116	- 4	35	30	-22	1011	1010
3 GMS. KEBILAC (MIXTURE OF KETOCHOLANIC ACIDS)	6	14	137	255	+105	1219	1401	+ 15	3000	767	+25	9	11	+22	133	122	- 9	26	26	-10		

\*C = Control; \*T = Treated.

\*\*This is in addition to Keto-Reactive Substances normally secreted.

\*\*\*C in this column for Bilron and Ox Bile (Wilson) represents the Control Basal Output plus the Cholic Acid fed, for example:  $1422 + 1500 = 2922$  in Case of 3 gm. of Bilron; and  $1455 - 1710 = 3203$  for 3 gm. Ox Bile (Wilson).

TABLE IV

Showing the effect of the administration of cholic acid in the form of natural ox-bile salts on the elimination of keto-reacting-substances in the bile

	No. of Dogs	No. of Tests	Vol. cc. Per Day	Keto Groups mg. Per Day	Con. Keto Groups Per cc.	Total mgrs. of Keto-reacting-Substances Per Day, Calculated as Tri-ketocholic Acid
Control; no return of bile or bile salts	15	55	126	52.6 ± 4.4*	0.41	252
1.5 gm. cholic acid*	9	34	190	72.1	0.38	393
2.5 gm. cholic acid	5	19	219	92.8	0.42	441

\*Contains no keto-reacting substances.

\*\*Standard error of the mean.

another was increased 55 per cent. Three grams of the oxidized bile acids were not observed to produce such variable responses, which confirms Riegel, Ravdin and Prushhankin (7). Using 5 gms. of the oxidized bile acids Schmidt, et al (8) observed a greater depression than we have, which is accounted for in part by the variation in dogs and by an inadequate number of tests, the importance of which was not realized at that time.

According to Reinhold and Wilson (15), when sodium dehydrocholate (Decholin, Sodium), is given intravenously to anesthetized dogs, the dehydrocholate largely replaces the cholates naturally present. According to our results obtained by oral administration to unanesthetized dogs, the degree of replacement of cholates by keto acids appears to be subject to considerable variation. In addition, as will be shown later, a considerable and variable portion of the oxi-

dized or keto bile acids given orally are not recovered as such in the bile.

*Comment.* The increase in cholic acid output when natural cholates are fed appears to be derived solely from the cholates fed. That is the administration of natural cholates does not appear to increase cholic acid synthesis by the liver. This will not be categorically established, however, until the cholates fed can be labelled in some way. There is no evidence that any of the bile salt preparations stimulated cholic acid synthesis and in this respect the oxidized products are not different from the "natural" or unoxidized products. For example, in order to increase cholic acid output by the liver, the oxidized bile acids (a) either would have to be reduced or their keto groups changed to hydroxy groups (Fig. 1), or (b) they would have to stimulate cholic acid synthesis from protein, according to existing views, in the liver. If either of these processes were known to occur, such knowledge would be of considerable biochemical interest. Our results indicate, but do not prove, that neither of these processes occurs. On the other hand the oxidized bile acids (a) may be absorbed and excreted in the bile as such, with or without replacing the natural cholates produced by the liver; or (b) some may be changed into cholic acid or some of the carbonyl groups may be reduced to hydroxyl and excreted and some may not be changed; or (c) the amount absorbed and carried to the liver may vary; or (d) the amount destroyed or stored in the body may vary. In an attempt to elucidate some of these possibilities, an attempt was made to recover in the bile the bile acids administered orally.

The recovery of orally administered bile acids in the bile. Having available a method for the determination of keto-reacting substances in bile that was reasonably quantitative, it was possible to determine the increase in keto-reacting substances in bile after the various bile acids were administered orally.

Recovery of cholic acid fed as natural Ox-bile salts and their effect on the keto-reacting substances in the bile. When 3 gms. or 5 gms. of "natural Ox-bile salts" are fed orally per day, approximately 90 per cent of the contained cholic acid is recovered in the bile, usually within 8 hours. This is shown in Table III, column C, and has been observed in previous studies (6). What happens to the 10 per cent that is not recovered is problematic. In Table IV is given the average value of keto-reacting substances normally present in dog's bile when the dog is receiving the diet, but no bile or bile salts. It is to be noted that when the "natural Ox-bile salts" are given the daily output of keto-reacting substances is increased. In Table V is

TABLE V

Showing variation in the same dog of cholic acid, keto-group and volume output per day from one control period to another over a period of six months (Rous-McMaster, biliary fistula method)

Test No.	Cholic Acid Per Day mg.	Keto Groups Per Day mg.	Volume Per Day cc.
1	2125	56.89	269
9	2124	60.82	226
5	2116	71.90	246
12	2053	92.17	248
10	2074	89.24	233
6	2059	80.08	252
2	1993	60.40	219
15	1976	124.77	217
7	1947	74.55	205
13	1935	101.50	225
8	1920	57.89	243
3	1919	70.43	234
11	1880	47.03	235
4	1852	65.04	255
14	1814	104.08	191
Average	1987	77.18	237

Volume output =  $237 \pm 20\%$  cc. per day.Cholic acid output =  $1987 \pm 9\%$  mg. per day.Keto-group output =  $77.18 \pm 52\%$  mg. per day; concentration per cc., 0.35 mg.

The per cent expresses the range above and below the mean.

the cholic acid output, the output of keto groups, and the volume output of bile in a dog on which 15 different 3 or 4 day control studies on the diet alone were made during 6 months. It is to be noted that although the volume output of bile and the output of cholic acid is relatively constant for a Rous-McMaster type of fistula, the keto output is subject to considerable variation in some dogs under basal conditions, and a correlation between fluid output and keto output does not exist. Other dogs (Table VI) are more consistent. However, when one averages the results of the effect of feeding "natural bile salts" orally (Table IV) on the keto output in a group of animals, it is found to be increased along with the fluid and cholate output. (The "natural bile salts" used contained only traces of keto-reacting substances). This suggested that some, possibly all, of the 10 per cent of cholic acid "lost" was oxidized either in the intestine before absorption or in the liver and excreted in the bile.

Accordingly our data was studied to ascertain whether the increase in keto groups in the bile after "natural cholates" were given orally might account for the cholic acid lost. The essential data on nine dogs are given in Table VII. Two questions arose. Should the milligrams of "lost" cholic acid (column A) be calculated as triketocholanic acid (column D)? Or should the "lost" cholic acid be calculated as oxidized conju-

gated acids, or as Dechacid (column E), since the "lost" cholic acid was given as unoxidized conjugated acids, chiefly glycocholic and taurocholic acids? The latter seems more likely. However, both calculations were made. If the "lost" cholic acid is oxidized and eliminated as pure triketocholanic acid, which is not likely, then 67 per cent of the "lost" cholic acid is accounted for. If the "lost" cholic acid is eliminated as oxidized conjugated tri-, di- and mono-ketocholanic acids, as Dechacid, for example, then somewhat more than the cholic acid actually "lost" (125 per cent) is accounted for. The variations between the individual dogs, however, do not warrant a definite conclusion. The variations may be due to the possibility that the liver may dispose of the "lost" cholic acid in different ways under different physiologic conditions. If so, the average of the group of dogs is more significant than the average of an individual dog.

Since the natural bile salts administered did not contain a significant quantity of keto-reacting substances, the increase in keto-reacting substances in the bile is due (a) either to the oxidation of some of the cholates fed, or (b) to an increased production of keto-reacting substances incident to the stimulation of the hepatic cells, or incident to choleresis. Since neither one of these two possibilities can be categorically eliminated, both have to be considered in calculating the recovery

TABLE VI

*Showing the control daily output of keto-reacting-substances in dogs' bile when bile or bile salts were not administered. The figures represent averages for a 3 or 4 day control period when nothing but the diet was given*

Daily Output				Daily Output			
Dog No.	Vol. cc.	Cholates mg.	Keto Groups mg.	Dog No.	Vol. cc.	Cholates mg.	Keto Groups mg.
1	131	1179	39.71	3	150	1365	36.57
11.1 K	146	1752	38.04	12.4 K	150	1455	59.14
	129	1638	39.08		146	1391	44.31
	135	1647	41.17		140	1470	34.28
	131		41.57		133	1220	48.91
3 A	151	2159	67.29	6	119	1523	32.81
15.0 K	140	1904	69.05	15.0 K	120	1452	27.59
	145	1914	63.12		120	1296	24.66
	176	1707	69.59		132	1240	28.42
5	151	2008	75.75	4	140	1638	37.41
11.5 K	158	1564	51.41	9.2 K	140	1302	45.98
	123	1402	35.74		151	1404	52.04
	131	1218	38.56		140	1302	39.71
				2 B	141	1770	54.15
				9.6 K	108	1606	77.00
2	282	2059	80.04	3 B	141	1875	103.40
19.0 K	248	2083	92.17		137	1754	172.63
	246	2116	71.99		127	1816	152.18
	243	1920	57.89	2 A	94	1636	30.51
	235	1850	47.03	11.0 K	99	1534	25.91
	233	2074	89.24				
	225	1935	101.5				

K. body weight in kilos.

in the bile of the orally administered oxidized or keto bile acid.

In fact, *three methods must be considered in calculating the recovery in the bile of the oxidized bile acid given orally. Method I.* It can be assumed that when an oxidized bile acid is fed, the oxidized acid replaces all the keto-reacting substances excreted normally in the bile. Then, the total amount of keto-reacting substances in the bile after giving an oxidized bile acid would represent the oxidized bile acid absorbed and excreted in the bile. For example, referring to Table VIII, column A, when 3 gms. of Dechacid were fed daily, 107.25 mgs. of keto groups were excreted daily. If all of these keto groups came from the Dechacid fed, then 107.25 mgs. of keto groups should be converted into Dechacid as follows:  $107.25 \div 0.112$  (11.2 per cent of keto groups in Dechacid) = 957 mgs. of Dechacid. To obtain the per cent recovered, the 3 gms. fed is divided into 957 mgs., and the result is that 31.9 per cent (Table IX) of the Dechacid fed was recovered. *This is the maximum recovery possible. Method II.* It can be assumed that when an oxidized bile acid is fed, the oxidized acid excreted does not replace any of the keto acid normally eliminated at any level of choleresis (see "b" in preceding paragraph). For example, when 3 gms. of Dechacid were fed daily, 107.25 mgs. of keto groups were excreted daily. However, we know that when 175 cc. of bile is excreted daily in response to "natural bile salts," 74.2 mgs. of keto groups are excreted daily and that the administration of 3 gms. of Dechacid was associated with an output of 175 cc. of bile. Thus, 74.2 mgs. should be subtracted from 107.25 mgs., or 33.05 mgs. of keto groups represent the Dechacid (295 mgs.) excreted in the bile. According to this method only 9.8 per cent (Table IX) of the Dechacid fed was excreted in the bile daily. *This is the minimum recovery possible. Method III.* It can be assumed that the increase in keto groups when "natural bile salts" are given is due to the oxidation of some of the bile acid or cholates given. Or, what amounts to the same

thing, it can be assumed that when keto bile acids are given, the increase in keto output above the control level represents the recovery of the keto bile acid. For example, when 3 gms. of Dechacid were fed daily, 107.25 mgs. of keto groups were excreted daily. The control keto output was 52.6 mgs. Thus,  $107.25 - 52.6 = 54.65$  mgs., or the administration of 3 gms. of Dechacid increased keto output by 54.65 mgs. Converting 54.65 mgs. into Dechacid, 487 mgs. of Dechacid were recovered; or the daily recovery of Dechacid amounted to 16.2 per cent. *This is the median yield.*

Since we believe the assumption on which Method III is based is theoretically most logical, is supported by the likely possibility that the increase in keto groups on giving "natural bile salts" is due to oxidation of the cholates given, and yields a median result, we have employed Method III to calculate the recoveries of the oxidized bile acids shown in Tables III and VIII.

*The recovery of oxidized conjugated bile acids, or Dechacid, amounted to 16.2 per cent when 3 gms. were administered orally as calculated by Method III.* When 5 gms. were administered, the recovery amounted to 14.3 per cent (Tables III and VIII). The average daily recovery of 3 gms. of oxidized unconjugated bile acids, or Ketochol (Searle), was 24.3 per cent; of 5 gms., 23.1 per cent. The average daily recovery of 3 gms. of Kebilac (Wilson Laboratories) was 25 per cent. The average daily recovery of 3 gms. of triketocholanic acid, or of dehydrocholic acid (Decholin), was 27.9 per cent; of 5 gms., 24.4 per cent. The recoveries calculated by the different methods are shown in Table IX. It is to be noted that the values obtained by Method II and III check well, and further that the recoveries of the various oxidized acids are almost directly proportional to the keto groups each contains. For example 87.6 per cent of 27.9 is 24.4, which checks well with the 24.3 per cent of ketocholanic acid (Ketochol) actually recovered. And 53.6 per cent of 27.9 is 15, which checks quite well with the 16.2 per cent of Dech-

TABLE VII

Showing the relation of cholic acid "lost" during one enterohepatic circuit to the increase in keto-reacting-substances excreted concurrently in the bile. From 1.5 gm. to 1.7 gm. of cholic acid were fed daily

Dog No.	No. of Tests	A. Mg. Cholic Acid Lost	B. % Cholic Acid Fed Recov.	C. Actual Increase in Keto Output Observed Mg.	D.* Max. Possible Keto Yield From "A" Mg.	E.** Possible Keto Yield From "A" as Oxidized Conjugated Mg.	F. % Cholic Acid Lost Calculated as Appearing as Triketocholanic C ÷ D	G. % Cholic Acid Lost Calculated as Appearing as Oxidized Conjugated Acid, C ÷ E
3	3	79	95.0	6.5	16.5	8.8	32.4	73.8
5	2	129	92.4	13.5	26.9	14.4	50.4	89.0
5A	3	163	90.4	27.8	34.0	18.3	81.1	151.8
6	1	262	84.7	10.3	54.7	29.3	13.1	24.5
4	4	452	74.0	28.7	94.0	50.6	30.4	56.0
2	12	110	93.0	30.0	23.0	12.3	130.0	244.0
3	3	0	100.0	20.7	0	.	.	.
5B	4	113	92.4	41.6	23.6	12.7	176.0	323.0
4	2	196	86.9	31.8	40.9	21.9	78.0	146.0
Total	34	1504	89.8	211.0				
Average		167	89.9	23.4	34.8	18.7	67.0	125.0

\*A x 0.209 = yield of keto groups calculated as triketocholanic acid.

\*\*A x 0.112 = yield of keto groups calculated as oxidized conjugated bile acids as they occur when natural ox-bile salts are oxidized.



A typical protocol of a single experiment for a 3-day post-bile-acid period is shown in Table X. In this instance 3 gms. of dehydrocholic acid (Decholin) were fed for 3 days. The output of keto-reacting substances had not returned to the control level 3 days after the administration of the keto acid had been stopped. The recovery (Method III) of the dehydrocholic acid fed, in this instance, during the period of administration was 27.5 per cent and during the total period, 30.6 per cent. In Table XII the results of another experiment show that (Method III) the administered keto-acid was still being excreted apparently for a period of five days after its administration had been discontinued. Some dogs return to the basal level of keto output within 48 hours after cessation of the administration of the keto acid. The variations are illustrated in Table XI. The total recovery of the various keto bile acids fed ranged in different tests in the different dogs from 15 to 50 per cent. The determination of the recovery for a 3 to 5 day period after cessation of administration of the keto acid only increased the per cent recovery by 6 per cent when the results on all the dogs are averaged. *The maximum recovery of the keto acid fed under any condition in all our tests was 52 per cent.*

*Comment.* It is obvious from the results of the foregoing experiments that the liver handles "natural Ox-bile salts" differently from the oxidized bile acids. The meaning of this is uncertain. The failure to recover in the bile more than one-half of the oxidized bile acids administered may be due in part to incomplete absorp-

tion (our dogs at no time had diarrhea) and in part to destruction or conversion to keto-hydroxy acids. The delayed excretion cannot be attributed entirely to slow absorption from the intestine. It suggests rather that the oxidized bile acids accumulate to a slight extent in the liver. To test this likely possibility it will be necessary to devise a test for quantitatively determining keto-reacting substances in liver tissue.

*The relation of "natural (unoxidized conjugated) bile salts" to the recovery of administered oxidized bile acids.*

It was thought that the administration of "natural bile salts" for a period after the oxidized bile acid had been given might increase the output and recovery of the oxidized bile acid. The protocol of such an experiment is given in Table XII. These and the results of two other experiments, when compared with the results of similar experiments like those recorded in Table XI, suggest, but do not prove, that "natural bile acids" given after a course of oxidized bile acids tend to increase the recovery of, or to "wash out" the oxidized bile acids. Further, experiments were not done because the difference was not sufficiently striking to warrant the time and labor that would be involved.

In the preceding experiments, the various bile acids were given to an animal maintained for at least 3 days under basal conditions or without receiving a bile acid of some sort. However, most patients that now receive bile salt therapy certainly are secreting some "natural bile salts" into the intestine. So, it is of interest to

TABLE XI

*Typical results on TOTAL recovery of administered oxidized bile acids calculated by method III*

Bile Acid Given	Amount Recovered During the Period of Administration 3 Days	Amount Recovered After Period of Administration	Total Recovered Mg.	% Recovery
5 gm. Dechacid				
Dog 1 8.4 K	1689	1873	3562	24
3 gm. Dechacid				
Dog 4 12.6 K	865	536	1401	15
3 gm. Ketochoh				
Dog 3 12.0 K	3039	1460	4499	50
Dog 1 8.4 K	3384	1149	4533	50
Dog 5 11.5 K	1809	140	1949	22
Dog 2 19.0 K	2652	541	4193	46
Dog 2 19.0 K	2976	164	3140	35
Dog 2 19.0 K	3216	375	3591	40
5 gm. Ketochoh				
Dog 2 19.0 K	5262	26	5288	34
	5613	194	5807	39
Dog 4 9.4 K	5046	117	5163	34
3 gm. Decholin				
Dog 3 13.0 K	2478	274	2752	30
Dog 5 11.5 K	746*	491	1237	20.6
Dog 4 9.2 K	2163	59	2222	25
Dog 4 9.2 K	2544	77	2621	29
5 gm. Decholin				
Dog 6 13.3 K	3573	134	3707	24
Dog 5 11.5 K	3370	473	3743	24

\*This was only for a 2-day period.

know what would happen to cholic acid output when an animal receiving "natural bile salts" is given in addition some oxidized bile acid. The typical results of such experiments are shown in Table XIII. The percentage recovery of both cholic acid and keto-cholanic acid is the same whether they are given separately or together. Although the differences observed in the recovery of keto acid are within experimental error, it appears as if the administered keto acid replaces the keto-reacting substances which increase after "natural bile salts" are given. *From a practical standpoint, however, there is no reason to suspect that the administration of an oxidized bile acid to a person who has a normal liver, which is already producing and secreting the natural conjugated bile acids, will interfere materially with the output of "natural bile acids."*

*Effect of bile acids on cholesterol output.* We have uniformly found in this and a previous study (6) that Ox-bile salts, containing no cholesterol, when given orally increase the total daily output of cholesterol in the bile. The increase is greater than the experimental error, which is 2 mgs. above or below the mean output. The oxidized bile acids, except dehydrocholic acid, or Decholin, also increased cholesterol output (Table III). Decholin, however, quite uniformly decreased cholesterol output. In an occasional test not more than a trace of cholesterol could be found. This was not due to a dilution error in the chemical method because at the same time an increase in the dilute bile obtained in response to ketocholanic acids (Ketocho) showed an increase in cholesterol output.

The only explanation of this interesting observation that has occurred to us is that Jones and Dolkart (16) have found that ketocholanic acids (Ketocho) are a somewhat better solvent for cholesterol than dehydrocholic acid (Decholin), a property that is due to some

unknown constituent of Ketocho. This suggests that when considerable dehydrocholic acid (5 gms. are relatively large doses) is passing through the liver cell into the bile, it does not carry cholesterol as does the other bile products used. However, the cholesterol does not accumulate in the blood, since dogs fed 5 gms. of Decholin daily for seven months showed normal blood cholesterol values.

The observation that unoxidized conjugated bile salts increase cholesterol output confirms previous observations (6, 11, 12). Kohlstaedt and Helmer (13), using convalescent biliary fistula patients, observed only a slight change in cholesterol output when 1-2 grams of "Bilron" per day were given. Although the "natural Ox-bile salts" increased cholesterol output in our experiments, they also increased cholic acid output so that the cholic acid : cholesterol ratio remained in the normal range. Thus, there is no danger of cholesterol precipitating and becoming a nucleus for a gall stone, when bile salts are administered.

*Effect on pigment output.* None of the bile acids studied had a significant effect on pigment output. The 25 per cent increase of pigment when 5 gms. of Ketocho was given to one group of animals is statistically significant for that group, but is neither physiologically significant, nor statistically significant if the mean for all our animals, 112 mgs., is used instead of the group mean of 109 mgs. (Table III).

*Effect of the various bile preparations on the non-volatile solids, viscosity of bile, and specific gravity.* Does the administration of bile salts actually "thin" the bile?

Bile is secreted iso-osmotically with blood, and is iso-osmotically concentrated in the gall bladder with an increase in specific gravity. It is interesting that choleresis was not accompanied by significant changes

TABLE XII  
*The recovery of an oxidized bile salt in the bile calculated according to method III*

Dog	Regime	Volume cc./24 Hrs.	Cholic Acid mgs./24 Hrs.	Cholesterol mgs./24 Hrs.	Pigment mgs./24 Hrs.	Total Solid mgs./cc.	Recovered Ketocholanic Acids Mr.*
1 8.4 K	Control						
	1st day	157	1350	6.0	142.0		
	2nd day	147	1308	8.2	128.0		
	3rd day	134	1256	9.6	115.0	31.0	0
	3 gms. No. 173 Ketocholanic Acids (Ketocho)						
	1st day	292	1606	13.7	82.3		
	2nd day	295	1431	11.4	68.6		
	3rd day	331	1400	13.6	52.6	30.0	3384
	3 gms. purified ox-bile salts (Wilson)						
	1st day	230	2599	14.4	84.2	35	320
	2nd day	215	2688	14.0	87.1	37	130
	3rd day	221	2696	15.0	93.0	37	250
	4th day	213	2662	14.9	91.4	37	281
	5th day	207	2665	14.3	74.7	39	168
	6th day	198	2617	13.3	73.0	41	7
	Total Ketocho recovered						4,533 mgs.

Total intake of Oxidized Bile Salt = 9.000 gm.  
Total output during feeding period = 3,384 gm. = 36.7%  
Total output during feeding period = 4,535 gm. = 50.3%  
Ketocholanic acid, % recovery = 50.3%  
Cholic acid, % recovery = 88.9%

\*This is in addition to keto groups normally secreted during the control period which amounted to 54.6 mg. per day.

in the specific gravity of bile. This is shown to be the case by the actual averaged data given in Table III. Thus, from the standpoint of specific gravity, bile salts do not "thin" hepatic bile. In this connection it is of interest to note that Wigodsky and Phibbs in our laboratory have observed no significant difference between the specific gravity of gall bladder bile of dogs that had received Ketochol and those that had received no medication before the bladder bile was studied.

The non-volatile solids were determined by drying an aliquot of the bile at 110° C. and 25 mm. Hg. pressure. The averaged data are shown in Table III. The administration of "natural Ox-bile salts," because they increase the cholates in the bile without proportionately increasing water, was expected to cause an increase in the concentration of solids in the bile. This effect is well illustrated in Table VIII, where the concentration of bile acids is calculated. The oxidized conjugated bile acid, Dechacid, did not materially affect the concentration of the bile. That is, the choleresis or increase in volume output is almost exactly proportional to the increase in output of solids (Table III). The oxidized unconjugated bile acids, Ketochol and Decholin, decrease the concentration of solids in bile decidedly. Thus, from the standpoint of the content of non-volatile solids, "natural" Ox-bile salts "thicken" the bile, and the oxidized unconjugated bile acids, Ketochol, Kebilac and Decholin, "thin" the hepatic bile.

The viscosity of the bile was compared at 25° C. with that of distilled water by determining the time required for the same volumes to flow between two points on a long slender glass tube. The average time for distilled water was 1 min. and 30 sec. The value for the control bile (no bile salts administered) averaged 4 min. and 15 sec. The value for the bile after the administration of "natural Ox-bile salts" was 4 min. and 50 sec.; for Dechacid No. 14 it was 4 min. and 30 sec.; for Ketochol, 3 min. and 40 sec.; for Decholin, 3 min. and 20 sec. Thus, from the standpoint of viscosity, the "natural Ox-bile salts" tend to "thicken"

the bile and the oxidized unconjugated bile acids, Ketochol, Kebilac and Decholin, definitely "thin" the bile.

It should be pointed out that the type of bile that we collected as normal controls was secreted by a normal liver and by an animal receiving an adequate diet. Its viscosity is not to be compared to that of a bile that is obtained under abnormal conditions. The bile obtained after administration of "natural Ox-bile salts" is very "thin" bile compared to that seen in the bile passages under certain abnormal conditions.

## DISCUSSION

The practical implications of these observations have been discussed in considerable detail elsewhere (17) under the topic, "The Rationale of Bile Salt Therapy in Biliary Tract Disease." One point was made in that article which we should like to emphasize, namely, that the selection of a bile acid for therapeutic purposes is not as simple as it might appear to be on superficial examination. This is at least true from an academic viewpoint when one considers the chemistry of the bile acids. Whether the chemical differences between the various bile acid preparations are of much practical therapeutic significance remains to be determined. However, it is clear from our work that the "natural Ox-bile salts" produce a bile quite different chemically and physically from that produced by dehydrocholic acid and unconjugated ketocholanic acids. And, if hydrocholeresis is the sole desideratum, the unconjugated oxidized bile acids, dehydrocholic and ketocholanic acids, are definitely preferable per unit weight.

We also desire to reiterate that we know of no direct evidence showing that any type of choleresis "flushes out the gall bladder." The bile ducts obviously can be flushed; but it does not follow that flushing the ducts will cause or be associated with a flushing of the gall bladder.

## SUMMARY AND CONCLUSIONS

1. The pertinent chemistry of the various bile acids has been reviewed in order to indicate that the differ-

TABLE XIII

Showing the effect of giving oxidized bile acids with natural bile acids on keto and cholic acid output

Procedure	Average Daily Output				Recovery of	
	Vol. cc.	Cholic Acid Mg.	Total Keto Groups Elim. Mg.	Keto Group Increase Due to Keto Acid Fed Mg.	Cholic Acid %	Keto Acid %
Dog 3, 13.0 K						
A. Control	130	1707	54.	179.0*		32.6
B. 3 gm. Ketocholanic Acid	282	1657	233.			
C. 3 gm. Ox-Bile (Wilson)	171	2738	86.5	130.5	82.0	23.8
D. 3 gm. Ox-Bile + 3 gm. Keto Acid (B - C)	282	2901	217. 217-54	163.*	85.2	29.7
Dog 1, 5.4 K						
A. Control	146	1268	52.5	201.4*		36.6
B. 3 gm. Ketocholanic Acid	296	1479	254.0			
C. 3 gm. Ox-bile (Wilson)	210	2653	90.	165.5	88.8	30.0
D. 3 gm. Ox-Bile + 3 gm. Keto Acid	332	2752	255.4 -52.6	202.8*	92.1	35.6
Dog 4, 12.6 K						

\*These values on the same dog are so close together as to suggest that the keto acid fed replaces the keto acid produced in response to the natural bile salt administration.

ent bile acids available for use therapeutically may affect the liver differently.

2. In this study three kinds of bile acid preparations have been used: (A) unoxidized conjugated bile acids as represented by the salts of glycocholic and taurocholic acids found naturally in Ox-bile (Bilron, Lilly; Ox-Bile Salts, Wilson Laboratories); (B) oxidized conjugated bile acids, as represented by Dech-acid (Wilson Laboratories) which is chiefly oxidized glycocholic and taurocholic acids; (C) oxidized unconjugated bile acids, being represented by Ketochol (Searle) and Kebilac (Wilson Laboratories), which contain a mixture of tri-, di- and mono-ketocholanic acids, chiefly the former, and the other being represented by Decholin (Riedel-de-Haen), which is practically pure triketocholanic acid or dehydrocholic acid.

3. The bile has been assayed chemically for cholic acid, keto-reacting substances, cholesterol, pigment, non-volatile solids, specific gravity, and viscosity. No phase of the investigation was considered complete until at least 10 tests on 5 dogs with a Rous-McMaster biliary fistula had been made.

4. Fifteen dogs receiving a control diet but no bile or bile acids secreted in the bile  $252 \pm 16$  (S.E. mean) mgs. of keto-reacting substances daily expressed as triketocholanic acid, or  $52.6 \pm 4.4$  mgs. of keto groups per day. This had to be determined in order to determine the recovery in the bile of any oxidized or keto bile acid administered.

5. On the average when an increase in bile volume output is produced by giving "natural" Ox-bile salts, a proportionate increase in the excretion of keto-reacting substances occurred. Since on the average 10 per cent of the cholic acid in the Ox-bile salts fed is "lost," it appears as if the increase in the excretion of keto-reacting substances comes in part, if not entirely, from the oxidation (ketonization) of the 10 per cent of cholic acid "lost."

6. On the average when unoxidized conjugated bile salts are given orally 90 per cent of the cholic acid is recovered in the bile and usually within 8 hours. However, when oxidized bile acids of any sort are given, only from 9 to 37 per cent are recovered daily by our method in the bile during the period of administration. After the administration is discontinued, oxidized bile acid is excreted from 1 to 5 days, giving a total recovery of from about 15 to 52 per cent. Thus, it is clear that the liver or body handles oxidized bile acids somewhat differently from unoxidized bile acids. What happens to the unrecovered oxidized bile acid is unknown.

7. The oxidized unconjugated bile acids, dehydrocholic acid (Decholin), ketocholanic acids (Ketochol and Kebilac) provoked a marked *hydrocholcrisis*, or

an increase in the output of bile having an increased water content and a decreased content per cc. of cholates, non-volatile solids, and a decreased viscosity. A truly "thin" bile is the result.

The oxidized conjugated bile acids, that is, conjugated ketocholanic acids, caused a moderate increase in bile volume output with but little change in cholates, water, non-volatile solid content and viscosity.

The unoxidized conjugated bile acids, taurocholic and glycocholic acids as found in Ox-bile, caused a moderate increase in bile volume output with an increase in total cholates, non-volatile solids and a slight increase in viscosity.

Thus, the combination of glycine or taurine with ketocholanic acid, suppresses the hydrocholcretic effect of the keto acid. This conclusion is tentative because pure bile acids were not used. It does not follow, however, that the conjugation of all ketocholanic acids will depress their cholcretic activity; neither does it follow that the oxidation of all cholanic acids will give them hydrocholcretic properties. This can only be settled by actual experiment.

8. The administration of the oxidized bile acids neither uniformly increases nor decreases the output of natural bile salts. The administration of "natural Ox-bile salts" (conjugated cholates) increases the output, but not the natural synthesis of cholates in the bile.

9. When oxidized bile acids are fed with "natural Ox-bile salts," the one does not significantly affect the elimination of the other in the bile.

10. The administration of bile acids does not significantly affect bile pigment output under the conditions of our experiment; cholesterol output was increased with all the bile acids studied except dehydrocholic acid. Five grams daily of dehydrocholic acid definitely decreased cholesterol output in the bile without significantly affecting the blood cholesterol level.

11. If one desires to flush the bile ducts (not the gall bladder) with a relatively copious quantity of thin bile then one of the oxidized unconjugated preparations of dehydrocholic acid or ketocholanic acids should be used. If one desires to increase the volume output of bile by the liver and at the same time increase its concentration in those bile salts that naturally predominate in human bile, then a preparation containing "natural Ox-bile salts" should be used. We have not yet studied hog's bile or hyodesoxycholic acid.

None of the foregoing statements are intended to be applied to the liver in hepatitis or during recovery from obstruction. We are skeptical regarding the wisdom of bile salt therapy under such conditions except for the purpose of improving intestinal absorption.

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## Notes on Some Recent Books on the Psychoneuroses and Minor Psychopathies

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ONE of the most trying problems of the gastro-enterologist, especially when he has a strong sense of devotion to the best interests of his patients, is what to do with those many nervous, psychopathic, and constitutionally inadequate persons who come to him for help. If it weren't for the coming of these persons to his consulting room every day, his life would be much happier and easier, and more often he could get away at four-thirty for a good game of golf. Time and again as he stays late in the office trying to help these problem-people he will wish fervently that there were some psychiatrist in his city who would take them off his hands, someone who would treat them sensibly, kindly and understandingly, and someone who would be willing to spend much time on them without adequate remuneration.

The problem is to find a man (1) who had good medical training and experience before he went into psychiatry, (2) who is not so blinded by the dogmas of Freudianism that he cannot study disease as he finds it, and (3) who is interested not so much in the hopelessly crazy asylum inmate as in the person who is worn out by foolish fears, compulsion neuroses, excessive irritability, and difficulties in adjusting to the problems of life.

The clinician can seldom send these patients to the type of psychiatrist who runs a sanatorium because they wouldn't be caught dead in his office, and they wisely object to going to his hospital to be thrust into contact with the insane. It would be of little use also to send the nervous, worried patient to the average neurologist because he is interested mainly in organic disease of the nervous system, and little inclined to spend time talking to a fussy woman who hasn't a patch of anesthetic skin or a "Babinski" to show for herself.

There is, of course, nothing of discredit in this to psychiatrists and neurologists—they have a perfect right to spend their time on what interests them, but still there remains a great need in every city of this land for well-trained, able and consecrated physicians who will help with the treatment of the neuroses, psychoneuroses, and mild psychoses. Unfortunately, only occasionally are men born who can do the job well, or who care to do it.

As I have already pointed out, such men must first be well trained in every branch of internal medicine so that they will know organic disease when they see it and will not start treating as a "neuro" the woman with exophthalmic goiter or the man with pains due to

widespread carcinomatous metastasis. The type of psychiatrist I envisage will meet his greatest need for sound medical knowledge and judgment when he comes to deal with those many patients whose anxiety neurosis or hysteria is *superimposed* on organic disease of heart or blood vessels or stomach.

Until this new type of psychiatrist is readily available, and doubtless for a long time after that, every clinician and every specialist should be prepared to understand and take care of all the neurotic and psychotic patients who come to him. In other words, the cardiologist should be fully prepared to treat the cardiac neuroses, the gastro-enterologist should know well the abdominal neuroses, and the urologist should know how to help the man with psychic impotence and "lost manhood."

Unfortunately there is little instruction being given in medical colleges today in the handling of this common type of disease. So great an effort is being made to turn out students who know the science of recognizing organic disease that little is being done about the art of curing neuroses. Because of this, when the young physician opens his office and discovers that a third of his patients have "functional troubles" and that his success in practice is going to depend largely on the skill with which he handles these people, he has to get busy and learn what he can from books.

I had to do just this some thirty-two years ago, and young physicians today may well find help in the books that I discovered then. I have listed some of them in chapter 7 of my book on "Nervous Indigestion" and others are mentioned in the last chapter of my "Introduction to Gastro-enterology." After looking through these chapters, the young graduate may want to read Dubois' "The Psychic Treatment of Nervous Disorders," the three little books by Weir Mitchell, some articles by O. W. Holmes, and Osler, and a little book by Peabody.

The most helpful writings that I have found in recent years are those of T. A. Ross. I was so charmed by his article on the psychoneuroses in the recently published seventh volume of Oxford Medicine that I eagerly sent for two of his books, "The Common Neuroses," and "An Enquiry Into the Prognosis in the Neuroses." Here is a man who sees the patients we gastro-enterologists so often see; he describes their troubles in simple speech, and he gives many hints as to what to do and what not to do with them.

Interestingly, Ross was not trained as a psychiatrist, and actually, as he wrote me, he regards himself as

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fortunate in having escaped such "training." During the seventeen years in which he was in general practice, he saw so many neurotic and psychotic patients that he felt compelled to learn all he could of their care. Eventually he became so interested in the borderlines of psychiatry that he specialized in this field and now he has become an outstanding authority in it. For years he was director of the Cassel Hospital for Functional Nervous Disorders, an endowed institution for the study of the psychoneuroses and mild psychoses.

In Great Britain Ross finds the same difficulty that we internists have here; he cannot get the physicians and surgeons on teaching hospital staffs to take any interest in the patient with the common borderline type of psychiatric problem. Yet these same physicians keep complaining that they cannot find qualified consultants to whom they can refer their neurotic patients. As Ross says, so long as the leaders in medicine and teachers in medical schools ignore this tremendous problem, the students and young graduates will ignore it also.

Following are some of the notes I made while reading Ross' book on "The Common Neuroses, Their Treatment by Psychotherapy." He feels sure that most of the treatment of functional nervous disorders will have to be done by the general practitioner. Obviously, if in a busy general practice the physician is to do this type of work, his methods of diagnosis and treatment must be simple and not too time-consuming.

While Ross believes that most patients can be treated successfully by the general practitioner, he admits that some are so hard to handle that they will have to be attended to by specialists, and some will be incurable even in the best of hands.

In most cases elaborate and lengthy methods of psychoanalysis are unnecessary; to use them in some cases would be like using a steam hammer to crack nuts. Furthermore, Ross has found that in many cases the technic does more harm than good. In some difficult cases it can, of course, be helpful, and we must all recognize our debt to Freud for many good ideas.

The physician must always remember that the psychotic patient believes in what he feels just as firmly as we, who are sane, believe in what we see and feel. Hence there is little use in arguing with such a person at length because it will only make him angry.

Many physicians tell a patient to use his will power and "snap out of it," but Ross doubts if a man can keep going on will power very long; it is like running an automobile with the starting battery.

It is wrong to speak of an imaginary pain. If one of us says he has a pain he either has it or he is a liar!

Ross wisely points out that, in dealing with these cases of nervous and mental disease, if the physician balks at spending two hours in taking a good history he will waste dozens of hours on futile and misguided treatment.

Many patients should be made to see that they should not demand at the start of treatment a definite diagnosis. Let them rest and mend their ways for a while and then see what symptoms are left.

Sir James Paget used to say, "The patient says that he cannot, the nurse says that he will not; the truth is that he cannot will."

To show a patient how real Ross thinks the symptoms are in spite of the fact that they are functional, he often points out that when a medical student at his first operation faints and falls to the floor, there is nothing imaginary about the fall, the unconsciousness or the ischemia of the brain. They are all real, and yet the trouble is a functional one, brought on by emotion. Similarly, when a finicky woman is nauseated and vomits at the sight of an inch worm in her salad, the symptoms are real enough, even if the stomach is normal.

Most important is Ross' injunction to physicians not to make the diagnosis of a neurosis by exclusion only. *It should be made because the symptoms are those of a neurosis.*

Unfortunately, the depression of manic depressive insanity can closely resemble that of neurasthenia. It is highly important that the differential diagnosis be made correctly because the prognosis is so different in the two conditions. The majority of purely neurotic patients, if they are ever to be restored to their places in society, should show decided improvement in a few weeks or months, but the man or woman who is in an attack of depressive insanity is likely to stay in it for months or years.

The patient with what appears to be an anxiety neurosis should be studied carefully and a searching history should be taken. Then if the physician is sure that the trouble is only a neurosis, the patient should be encouraged to do more than he thinks he can.

Ross does not believe in "borderline" states. He believes there is a great difference between the depressed neurasthenic and the depressed psychotic, and that the disease of the one will not shade over into the disease of the other. As proof of this he notes that a follow-up study showed that only 5 per cent of 1043 neurotic patients became insane in the period of from three to ten years following their examination. This is the percentage of all persons in New York State who get committed at some time during life. Instructive also is the fact that few neurotic patients commit suicide, while, as everyone knows, many depressed psychotics do. The neurotic commonly blames all his troubles on overwork, while the psychotic denies that he has been overworked. Actually, the psychotic can sometimes work on without any feelings of fatigue. Ross doubts if many really sane persons can overwork sufficiently to do themselves serious harm.

Helpful diagnostically is the fact that in cases of true melancholia the patient is not made any sadder by news of the death of a loved one or by any disaster. In order to see if a patient is insanely depressed, Ross sometimes presents a group of colored fabrics and asks that a choice be made. The depressed patient will refuse to make this choice because, as he says, all the colors are indifferent to him. Also helpful diagnostically is the tendency of the psychotic person to say that his troubles are all his own fault. Furthermore, the sins that he blames himself for are usually peccadillos. The psychotic talks slowly, while the neurotic is more lively and is likely to change his mood more quickly. The psychotic is more concerned with his mental depression than with his bodily distresses, while the neurasthenic is more worried about his aches and pains than he is about his psychasthenia. The psychotic is often so apathetic and unconcerned about

himself that the family has to bring him to the physician and then give the history. The neurasthenic loves to go to doctors and to talk about himself. If a patient seems to like to confess to sexual sins this suggests a psychosis!

Ross describes hypochondriasis as a fixed idea of ill-health, which is irremovable. The patient is usually an elderly man who states that some part of his body is seriously diseased. He is constantly seeking medical aid, and he will cheerfully undergo any type of treatment recommended, no matter how painful or troublesome it is. He is an unusually "good patient" who carries out every new treatment to the letter, in spite of the fact that it does not do any good. After years of going to physicians, suddenly the illness will shift to another organ, and the first one will seem then to disappear from consciousness. This type of patient is incurable, but he should be humored and taken care of by the physician, if only so that he will not fall into the hands of the quacks and be fleeced. In all other respects these patients are usually shrewd, intelligent, and sensible people. Many become wealthy, perhaps because of their meticulous ways.

There is another type of hypochondriac who is really slipping into insanity when he begins to go the rounds of physicians. He is certain that he has cancer of the stomach or intestinal obstruction or other serious disease, and he often talks physicians into operating on him again and again for an intestinal obstruction which is poisoning him and destroying his brain.

The first interview with a nervous patient is the most important one of all, and if the physician is short of time he should postpone the interview until he can give at least an hour to it. These patients always have much to say, and they should be allowed to say it in their own way. Extensive notes should be taken. As Ross points out again and again, hours of time which the physician commonly wastes on futile treatment could have been saved if he had only spent an hour or two taking a good history at the beginning.

It is not always the worry that does a patient harm; the important point is how the worry is regarded. For instance, a boy may worry about masturbation, but this worry will not do him any harm if he has never been told that masturbation is a terrible sin and that it will destroy his brain and his sexual power. A man may worry about cancer, but this will not injure him much unless the recent death of a relative with cancer has convinced him that he too must die of it. Most people worry about a discomfort, not because it is very bothersome, but because they don't know what is causing it or what it will lead to. The physician could save himself hours and hours of wasted time in treating patients if he would only take the trouble to find out at the beginning *why* the patient came to consult him, *what* he or she feared, and *why it was feared so much*. This is particularly essential when dealing with Jewish patients who tend to become obsessed by fear of the diseases to which relatives have succumbed.

The physician must get a good biography of the patient, and no third person should be present during the first interviews. The physical examination must be thorough because it is an important vehicle of psychotherapy.

Ross states his belief that of all mistaken policies of physicians that of lying about a serious lesion is the worst. He thinks that patients with cancer are

best told because they will soon find out anyway. Someone will let the cat out of the bag.

As Ross points out, innumerable neuroses are produced by the type of physician who, in order to keep a line of retreat open, gives a vague and straddling opinion. When faced by a man with a chronic cough he should decide either that active pulmonary tuberculosis is present or that it is absent. To diagnose "weak lungs" may enable the physician to say later, "I told you so," no matter how the case goes, but this sort of diagnosing is cruel and unfair because it so often gives rise to an anxiety neurosis. As Ross says, not to promise a cure when one should do so is quite as wrong as to promise it when one shouldn't.

Very true is Ross' statement that it may be far more important to show a patient *how he fell ill* than to give a name to his disease.

Ross has much to say about the need for bolstering the self-respect of patients suffering from hysteria. Great damage can be done by accusing them of shamming. One must never treat them harshly, because they do believe in their paralyses and pains. To show how thoroughly a hysterical person can be self-deceived, Ross tells of a capable superintendent of nurses who, after a slight injury, drifted into a disabling compensation neurosis. She was so thoroughly taken in by her hysterical disabilities that in her efforts to get well she sacrificed a mouthful of good teeth. Finally Ross cured her by making her see what she was doing, and by persuading her to give up the small compensation payments she was receiving. Actually, it was hard for her to see that the payments were so much less than the salary she could earn by working that it was much to her advantage to get well. Like all these patients, she wanted that compensation for the principle of the thing, and she had great difficulty in facing facts and doing what was sensible.

It must be remembered also that a patient with severe organic disease may be hysterical or may actually be malingering in order to get sympathy or better care. Thus, Ross tells of a man with carcinoma of the pancreas who once took to his bed and feigned intense pain in order to make the doctor pay more attention to him. Interestingly, Ross says that outside of insurance practice, this man was the only true malingerer he ever could recognize in his practice.

In all cases of hysteria the physician must of course cure the symptoms with psychotherapy, but this is not enough. He must go on to uncover the psychic problem that brought on the paralyses or anesthetics or pains. He must find out why the patient became ill. The hysterical person believes in the reality of his paralysis, so to cure him one must make him lose belief in it. Then he will move the limb by himself. Later, he must be made to see clearly why he fell ill and why he was cured, if only so he will not slip back again.

Unfortunately, the cure of a hysterical disturbance can upset a patient badly, especially during war time. An officer who is talked out of a hysterical paralysis or blindness is likely to feel that he was a coward when his nervous system took refuge in illness. Then if he is to get back his self-respect, he must be given a good explanation of the situation. He needs to be told that he got his disease in good faith and because of an inherited type of sensitive nervous system. He wasn't malingering. Unless the physician takes the time to

make these things clear, the hysterical patient who has just been cured may promptly take refuge in a worse type of neurosis, or in the case of a sensitive officer, he may commit suicide.

Ross believes it is the physician who takes the enlightening history who should work the cure of a hysterical manifestation. Usually it is well to try for a cure at the first interview. Often it can be worked then more easily than it can be later. In some cases all one needs do is to explain the situation to the patient and next day he or she will come back well.

As every good physician knows, a traumatic neurosis is rarely curable while the patient has a lawsuit pending. Patients with such neuroses are not malingering, but they cannot give up their symptoms so long as they need them to win the suit. As a general rule it is cheaper for the insurance company to pay such persons a lump sum than to go on paying doctors for attempts at a cure.

The compulsion or obsessional type of neurosis is the most difficult to cure, and many of the patients just cannot be helped by any method of treatment now known.

Many persons with a mild depressional psychosis do not need to go to an asylum. They can be cared for in their homes. The treatment is that of expectancy because nothing is known that will definitely shorten the attack. The physician must, however, at each visit suggest something to do so as to keep up hope in patient and family.

When patients are in an excited stage of a psychosis Ross advises the giving of paraldehyde in doses of 3 drachms in water. It is no use trying to cover up its taste. Sulfonal can be given in 20 grain doses, and chloral in doses of from 25 to 30 grains with 30 grains of bromide. Even larger doses are used in asylums.

In chapter 10, pages 562 to 634, in the seventh volume of *Oxford Medicine*, Ross has many more interesting things to say. He points out how emotional reactions, harmless in themselves, can lead to disease, especially when the patient is easily frightened and has come to believe that some organ such as the heart is seriously diseased. As he says, too often the natural tendency to fear is increased by the unfortunate statements of physicians. Even when the physician does not say that the heart is diseased, he will produce a bad psychologic effect by advising that the patient go easy on stairs. Often the less the patient exercises the more palpitation he is likely to have, and the more palpitation he has the less likely he is to exercise. A vicious circle is thus set up which can be broken into only by the physician who insists flat-footedly that there is no disease in the heart and that the patient must not try to spare it.

Most patients when told that their troubles are functional promptly assume that by this the physician means that they are imaginary. This is most unfortunate. As Dr. Ross points out, the soldier who is seized with diarrhea when he has to go over the top is in exactly the same physical condition as if he had taken a large dose of salts. The woman who gets palpitation of the heart when she is angry has it exactly as if she had exophthalmic goiter. The physician must make every effort to show the patient that his symptoms are real, even while he insists that the organ which is misbehaving is sound.

It is most unfortunate to give a patient the idea that his palpitation is imaginary if only because this leaves him with the conviction that the physician does not understand the situation. Furthermore, the patient is the more frightened because he feels that he has a new disease unknown to science, and therefore probably incurable.

To show how under adverse circumstances one man will develop a neurosis while another escapes, Ross tells of two young men who had an old harridan of a mother who did her best to dominate both of them and to keep them from ever marrying. One brother held his own and had no trouble, while the other succumbed and took refuge in a neurosis.

An interesting point made by Ross is that the physical conditions which are usually held responsible for a neurosis are always trivial in nature. Thus, it is retroversion and not cancer of the uterus that is supposed to cause "nerves," and it is a small astigmatism and not a big one that is supposed to cause nervous headaches. Similarly, during the war of 1914-1919 it was the unwounded or the slightly wounded soldier who developed a neurosis.

Ross classifies neuroses into anxiety reactions, hysterical reactions, and obsessional reactions. Some persons have phobias and feelings of unreality without any physical troubles. When trying to judge the value of phobias there is one interesting point which will differentiate those of the neurotic and those of the insane. The neurotic person knows that his phobias are not real, while the insane person believes that they are.

Ross tells of a way to help those persons who worry themselves sick about sins that they only thought of committing or fear that they may have committed. The commonest worry of this type is that of the deeply religious man who feels that he has committed adultery in his heart (Matthew 5:28.) As Ross points out to these patients, since good intentions which are never carried out are not noticed in heaven, bad intentions which are never carried out are similarly disregarded by St. Peter!

Ross does not agree with the physician who says proudly that he can get all the information he needs from a nervous woman in a quarter of an hour by keeping her from wandering from the point. Ross believes that by keeping the woman from wandering the physician is likely to miss really important information. As he says, the nervous patient must not only be allowed to give the history in a rambling way, but he should be encouraged to do so. He must ramble along and tell all about himself and his illness and his troubles and unhappinesses. The story may have to be straightened out later, but that should be done by the physician.

Time and again after a long history has been taken and retaken and all the examinations have been made, the secret back of the whole trouble will suddenly come out in a chance remark. Without this secret in his possession the physician's treatment would be misdirected and his time wasted.

The physician must learn to listen patiently, and the history must often be obtained during several sittings of an hour each. Finally, this history which is so essential if the right diagnosis is to be made, is also the main instrument of treatment. The treatment



cannot be logical or successful unless it goes to the secret root of the trouble. It is essential also that the doctor use good judgment in deciding what is important and relevant in the physical and laboratory findings. He mustn't swallow all of these reports uncritically as so many physicians do today.

It is most important that the physician note the patient's attitude toward his illness. The patient with organic disease is often uninterested in his symptoms; he makes light of them, and his family has to drag the story out of him. In the physician's office they will have to give the history because he will not remember any suffering. Finally, he may refuse treatment. The neurotic patient goes to the opposite extreme; he is more interested in his illness than in anything else; he gladly sees many doctors, and he searches for the best he can find. He may be desperately anxious to get his doctor to understand how important the illness is.

Some physicians may think that the difference between a psychosis and a neurosis is that the psychosis is worse, but as Ross says, there are many psychotics who are walking about and conducting their business cheerfully, while many neurotics get so sick that they can't work, and many take to their beds.

Ross gives more suggestions that will be helpful in the differentiation of depressed insane patients from neurotic ones who are discouraged. Apathy is common in the psychotic, but not in the neurotic. The psychotic patient will not weep, while the neurotic one may. The psychotic cannot be made to laugh, while the neurotic may be made to cheer up, and he will often laugh at a joke. The psychotic is uninterested in everything, including his own state, while the neurotic is anxious about himself and his relatives.

Ross refers to the type of woman described by Robert Hutchinson who wants operations on the abdomen and has several performed without any benefit. Ross believes, and I am sure rightly, that these conditions are psychogenic and not curable. They are due to a psychosis rather than to a neurosis.

Ross points out that the physician who hopes to help people with an anxiety neurosis must never seem to be in a hurry. The first interview should last for an hour, and it is the most important one. If this interview proves disappointing to the patient, harm may have been done which can never be repaired by that particular physician.

In the matter of diagnosis, "Unsuresness spells failure in treatment." "Doctors who sit on the fence, who are always guarding themselves against somebody's saying later that they made a mistake, are great creators and confirmers of neurosis. One of the things that every doctor must be on guard against is guarding his own reputation. Let it take care of itself." Often the physician must act like a quack and promise a cure.

The physician should see the patient the day after he has used psychotherapy to see that what he said hasn't been mixed-up and confused. Often it helps to have the patient write out his impressions of what the physician told him. The patient with a purely nervous dyspepsia should never be given a diet but should be told to eat everything he pleases or that he has found he can digest comfortably.

When it comes to the care of the patient in the hospital it is highly important that the nurses be trained to express no opinions. If there is any differ-

ence between the opinion of the nurse and the physician, the hair-splitting and cross-examining type of patient will make the most of it. Only one person can practice psychotherapy at one time on one person, and the tendency for nurses to take a hand in the game is great.

Ross states that trauma is rarely followed by neurosis unless the man or woman hopes to make money out of it. Occasionally a neurosis will be started and later clung to for the purpose of teaching some disliked doctor that he was wrong in his opinion or brutal in his treatment. It is never easy to get patients to see the harm that they are doing to themselves in this way.

Another helpful book on the problems of nervous and depressed patients is Sadler's volume on the "Theory and Practice of Psychiatry." Here the gastro-enterologist will find good descriptions of those troubles which he sees every day. He will find in simple biblical English descriptions of the problems of the nervous persons who fill his waiting-rooms, and much thoughtful and helpful and detailed information as to how these problems can often be solved. Here is a book on psychiatry written for the general practitioner, the internist, and the gastro-enterologist. It is written so simply that the busy physician who comes home tired at the close of the day need not fear that the text will be too heavy and too indigestible for him.

As one might have expected from all this, Dr. Sadler did not get into psychiatry by the usual route through training in an insane asylum. During years spent in surgical practice he became so impressed with the numbers of his patients who needed, not the abdominal operation they sought, but help with problems of adjustment to living, that he stopped operating and gave up all his time to the helping of those unfortunates who so need the guidance of a psychiatrist or of a wise philosopher and physician.

It is a sad fact that today many a half-crazy woman gets herself operated on time after time simply because she insists that the queer hallucinations of sensation in her abdomen are due to intestinal obstruction which must be relieved promptly if her brain is not to be destroyed by the toxins arising in the stagnating intestinal contents. If she were only a little crazier, so that she would state that the writhing sensations in the abdomen were due to the presence of a snake, the true nature of her trouble would promptly be recognized, but because she speaks of pain and intestinal obstruction it rarely occurs to her medical attendants that, while sensible in most things, on this point she is insane.

As Sadler points out, the psychiatrist who would be of most service to the practicing physician needs to pay particular attention to the many neurotic and emotional states and to the disturbances of personality. In his book, Sadler takes up one after the other the various technics of examination and treatment; the personality problems of childhood, adolescence and adult life; the neuroses, the psychasthenic states, phobias, inadequacies, compulsions, inhibitions, mild depressions, neurasthenias, fatigue neuroses, anxiety states, sexual neuroses, occupational neuroses, hypochondriasis, the hysterias of various types, the dissociations of personality, and finally, the psychoses and their treatment. The book runs to 1231 pages. It

would be most helpful if in medical colleges today the students could be given time for reading this book and excused from learning the technics of many laboratory tests.

Another book which every young physician starting out in the practice of medicine ought to read and re-read is William R. Houston's "The Art of Treatment." It is full of helpful observations and wise suggestions for the handling of nervous patients. There are many paragraphs that are worth quoting. For instance, "Drugs are a poor camouflage for psychotherapy. Your psychotherapy will gain in precision and vigor if employed without placebos."

As Houston points out, so much of the trouble with most patients is fear, and the physician is greatest when he is casting out fear. Surely we physicians should not so often cause fear as we do. When the

quack cures, he does it usually by combating fear and convincing the patient that he is to recover.

How true it is, as Houston says, that many patients are forever talking about their symptoms. They are tremendously interested in them, but when the question comes up of doing something vigorous to combat them, interest wanes.

There is no doubt that the successful psychotherapist must always be born with the gift for influencing and leading and dominating the sick for their own good. But much of the art can and must be learned from experience. The wise physician will always learn all he can from those rare books that appear occasionally, embodying much of the accumulated wisdom of some unusually keen observer and able teller of what he has seen.

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WE believe the readers of this Journal will be interested in seeing from time to time abstracts or translations of some of the classic articles of gastro-enterology. Certainly every specialist and teacher who hopes to be a leader must know well the literature of his subject and the way in which that literature developed.

In the field of experimental ulcer there are a few early papers that are still of some interest today because the authors seem to have been the first to wonder if the mucosa of the jejunum and ileum might not be more vulnerable to attack by gastric juice than is the mucosa of the stomach and duodenum.

In 1893 Matthes got a glimpse of the important idea that the sensitiveness of the intestinal mucosa to gastric juice varies with the distance from the pylorus. He also saw that the natural resistance to acid of the mucosa of the stomach and bowel can be exhausted after minutes or hours of contact, and he noted that a mixture of hydrochloric acid and pepsin is more damaging to the mucosa of the bowel than is normal gastric juice of the same pH but containing some buffering substances.

In 1908 and 1913 Katzenstein showed again by transplanting bits of bowel into the wall of the stomach that the duodenal mucosa is more resistant than is the mucosa of the more distal parts of the small bowel. In 1909, Bickel, with the help of an operation somewhat similar to that of Mann and Williamson (1923) threw gastric juice into the first portion of the jejunum and found, as they did later, that perforating ulcers soon developed and killed the animal.

Another paper which can still be of interest to us gastro-enterologists today is that of Langenskiöld,

who in 1913 repeated the work of Matthes and largely confirmed it. Unfortunately he did not do as many experiments as he needed to be sure of his results. One of the most interesting of his observations and one that was discovered independently later by Mann and Bollman was that when a dog was fed, something went into the mucosa to make it more resistant to the attack of hydrochloric acid and pepsin. Langenskiöld showed that this substance might well be peptone. The importance of this observation will be evident to all of us who have to treat patients with ulcer by giving food every two hours. We see now that this food can help not only by buffering the acid but by protecting the mucosa.

It has long seemed to me that more attention should have been paid to this discovery. Perhaps in the treatment of ulcer a drip of peptone would be more effectual than are the antacid drips now used. Perhaps a drip of peptone used immediately after the performance of gastrojejunostomy or partial gastrectomy would save patients from getting a jejunal ulcer. Perhaps it would tide them over until the jejunal mucosa could get adjusted to the injury produced by the gastric juice.

In 1923 there appeared the highly important work of Mann and Williamson, who showed that in the dog, the jejunal mucosa is so vulnerable to the attack of unbuffered gastric juice that when the jejunum is attached to the pylorus, after the duodenal juices have been drained into the ileum, practically all of the animals will die of a perforated jejunal ulcer.

In 1932 Mann and Bollman showed much more clearly than Matthes and Langenskiöld had that if unbuffered gastric juice is left too long in contact with the gastric or the intestinal mucosa, the resistance of the tissue is exhausted and inflammation and finally

ulceration result. They showed also the great vulnerability of the jejunum and ileum to gastric juice.

Recently (1939) Florey, Jennings, Jennings and O'Connor have again shown the greater resistance of the duodenum to hydrochloric acid as compared with the jejunum and ileum.

With these thoughts in mind, I welcomed this translation which Dr. Lerner made of the more important parts of Langenskiöld's seventy-four page paper.

The majority of investigators believe that the gastric juice plays an important role in the formation of peptic ulcers, but some admit that there are other contributory factors at work. Some assume that digestive fluids do not attack living tissue, and hence an ulcer forms only when an area of mucous membrane has become necrotic. Others believe that the gastric mucosa possesses a specific defense against the gastric juice which other tissues do not have. When there develops an imbalance between this defensive mechanism and the digestive power of the gastric juice an ulcer forms.

In order to explain the formation of small areas of necrosis men have postulated:

(1) Disturbances in circulation, caused by degeneration of blood vessels, by emboli, thromboses, spastic contractions of small arteries or by blockage of veins, the latter resulting from contraction of the musculature of the gastric wall.

(2) Lesions of the mucosa produced by trauma, mechanical, chemical or thermal.

(3) The action of bacteria.

(4) Bacterial emboli.

(5) Toxins excreted by the stomach.

(6) Nervous factors.

(7) Changes in the composition of the blood.

Concerning (1):

Virchow believed that gastric ulcer should be considered as due to an infarct following blockage of the circulation in one of the gastric arteries, but he failed in attempts to produce ulcers by ligating a gastric artery. Similar attempts of L. Muller, Roth and Litt-hauer were also unsuccessful.

Fibich and Clairmont reported the production of ulcers in some such experiments. Cohnheim succeeded in producing large crater-like ulcers by injecting lead chromate into the gastric arteries. All of these ulcers healed within three weeks. Similar ulcers were produced by Panum, who used small wax pellets as arterial emboli.

By injecting dermatol or emulsions of India ink, Payr was able to produce emboli in the finest gastric vessels. As a result of these, hemorrhages, erosions, and occasionally large ulcers developed in the mucosa. These ulcers healed rapidly. Payr was able to produce chronic ulcers by intravascular injections of warm salt solutions, dilute formaldehyde or dilute alcohol. These experiments, while showing that destruction of the finer blood vessels can produce gastric ulcers, did not prove anything as to the usual pathogenesis.

Only in rare cases of ulcer could Merkel show changes in the gastric blood vessels. Korte did not see any changes in the smaller vessels of the gastric wall around a number of operatively removed ulcers.

A big objection to Virchow's concept of the pathogenesis of ulcer is the fact that most ulcer patients are not at the age in which vascular changes are usually found. Kleb attempted to get around this ob-

jection by assuming the presence of spasm in the small arteries in the gastric wall. This assumption later on received some support from the discovery of Rosenbach that adrenalin injected into the gastric wall caused ulcers.

Key attributed ulcers to venous stasis resulting from obstruction of the veins of the gastric wall by spastic contracture of the musculature of the stomach, and Talma claimed to have produced ulcers by stimulating the vagus nerve and thus producing a spastic contraction of the pyloric antrum. Curiously, Von Yzeren ascribed the ulcers which he saw develop in rabbits following subdiaphragmatic section of the vagi to this same mechanism of muscular spasm.

Concerning postulate (2):

Leube, Lebert, Kronlein and others mention cases of ulcer which followed trauma to the abdomen. Ritter produced such trauma in anesthetized animals in an attempt to produce gastric ulcer but obtained only submucous hemorrhages. Quincke and Daetwyler, using dogs, made a big gastric fistula through which they produced defects in the gastric wall by means of chemical, thermic, or mechanical insults. Without exception, these defects healed within 15 to 30 days. Only in animals which were made anemic did they persist for a somewhat longer period of time.

Matthes found that large mucosal defects were covered sooner because of a contraction of the gastric wall. In order to avoid this mechanism and to keep the whole base of the mucosal defect in contact with the gastric juice, he first sewed the gastric wall to a glass ring to keep it taut. Still the mucosal defect healed in few weeks. By giving the dogs 0.56 per cent HCl he was able to somewhat postpone healing in some of the animals.

Decker, using dogs, succeeded twice in producing an ulcer by giving the animals by stomach tube a mush heated to 50° C. According to Sternberg, in guinea pigs ulcers appear almost always following the introduction of 96 per cent alcohol into the stomach. These ulcers heal, however, within three weeks.

Concerning postulate (3):

On examining a number of ulcers, Bottcher found the base covered with bacteria, and hence ascribed to them a role in the production of the lesion. Korte found bacteria only in putrescent and perforating ulcers, and not in fresh or uncomplicated ulcers. According to Bloch, the calf frequently has chronic ulcers in that part of the stomach which contains pepsin and hydrochloric acid. These ulcers never contained bacteria.

Concerning postulate (4):

Letulle produced ulceration of the gastric mucosa by injecting subcutaneously dysentery bacilli; he produced also ecchymoses of the mucosa by intraperitoneal injections of staphylococci. Neumann also considered the theory of the bacterial origin of ulcer as the most probable one.

Concerning postulate (5):

Nauwerck and Sick pointed out that necrosis of the gastric mucosa might be produced by bacterial toxins.

Concerning postulate (6):

Ebstein and Schiff noted the development of gastric ulcers in animals with extensive lesions in the central nervous system. Dalla Vedova was unable to produce ulcers by vagotomy but did succeed by extirpating the

celiac ganglia and by severing the splanchnic nerves. Donati, however, was unable to produce ulcers by either of these two methods. Following nerve injury the ulcers seen were usually small and multiple.

Concerning postulate (7):

As has been mentioned above, Quinke and Daetwyler were able to postpone the healing of defects in the mucosa by making the animals anemic. Silbermann claimed to have produced chronic and even perforating ulcers by injuring the gastric mucosa in animals suffering from hemoglobinemia following the injection of pyrogallol. Litthauer confirmed this.

From the above short summary it may be seen that ulcers in the stomach may be produced in many ways, but such ulcers heal rapidly and therefore cannot be compared with the chronic ulcers of man. Only the ulceration resulting from destruction of the finer blood vessels of the gastric mucosa as produced by Payr is somewhat comparable to that of man. Unfortunately for Payr's theory, extensive vascular changes are usually not found around the ulcers of man.

The question then is: What is the nature of the predisposition? How does the normal stomach resist the action of the gastric juice, and how is this resistance overcome? Some assume that it is overcome by an excessive acidity of the stomach, but this is not always true. Let us see how the stomach protects itself. It may do so perhaps with the help of:

- (1) The gastric mucus.
- (2) A resistance of the epithelium to penetration by the gastric juice or strong regenerative ability of the epithelium.
- (3) The alkalinity of the blood circulating in the mucosa. It has been assumed that the blood of the gastric mucosa is more alkaline than that of other organs because of the secretion of HCl.
- (4) The presence of an "antipepsin."
- (5) The backflow of pancreatic juice, bile, and intestinal juices into the stomach.

Weinland, Danilevski, Hensel, and Blum and Fuld caused excitement by reporting the discovery of antipepsin in the gastric mucosa, but later research led to the abandonment of the idea. The experiments designed to show a greater resistance of the stomach to peptic digestion as compared with other organs were begun by Claude Bernard. He poked the legs of a living frog through a gastric fistula into the stomach of a dog, and decided that since they were rapidly digested, the epithelium of the stomach must possess a special resistance to digestion by hydrochloric acid and pepsin. Matthes maintained that the legs were digested not while they were alive but after their cells had been devitalized by the hydrochloric acid. In support of this concept, Matthes pointed out that live frogs are not digested by solutions of strongly active alkaline trypsin or solutions of pepsin activated with acids such as uric and hippuric, which are not so injurious to tissues as is hydrochloric acid. Dead frogs were rapidly digested by such solutions. Later, when Frenzel complicated matters by showing that the leg of a living frog could be digested in alkaline solutions of trypsin, Matthes answered that in these experiments glycerin had been used, which was injurious to frog tissue even in high dilutions.

When Newman introduced the leg of a frog into the stomach of another frog, the leg was not digested.

Pavy put the ear of a living rabbit into the stomach of a dog and found that it was digested.

Katzenstein sewed intestine and spleen into an opening in the stomach, exercising care to avoid circulatory disturbances, and found that the inserted organs were digested. Kathe obtained similar results. Later Katzenstein repeated these experiments and found that no digestion took place if special measures were taken to preserve the circulation in the transplanted organs. Viola, Gaspardi, Marie and Villandre obtained similar results. Later Bickel extirpated the duodenum of a dog, transplanting the common duct and the pancreatic duct and anastomosing the jejunum to the stomach, and found that after several weeks the dog was dead with a perforating ulcer in the upper jejunum.

With the view of contributing to the solution of these and other related questions, I undertook the experiments which I will now describe.

### EXPERIMENTAL WORK

In formulating plans for my work, I started from a thought which I later found had previously been expressed by Hari, and in a somewhat modified form by Palermo. Kolesterol also mentioned it in 1911. In most places where one sort of epithelium goes over into another, one often finds islands of one type scattered in the sheet of the other type. Islands of intestinal epithelium are found in the stomach, and if these islands should be less resistant to the digestive action of gastric juice than is the gastric mucosa, they might serve as starting points for ulcers. This theory might explain the marked hereditary disposition to gastric ulcer which was pointed out by Huber and Czernecki.

However, during the course of my work, a number of new ideas came to me, ideas which pushed this island hypothesis into the background. Incidentally, the studies of Lange and Saltzman showed that these islands need not always be congenital but are sometimes the result of pathological changes, as in cases of gastritis.

While testing the island hypothesis, it was first necessary for me to answer the following questions:

- (1) Have all living tissues an equal resistance to the gastric juice, and more particularly, is there a difference between the resistance of gastric and the intestinal mucosa? Also are the several parts of the bowel equally resistant?
- (2) If differences are present, where is the boundary between resistant and digestible parts?
- (3) Do the resistant parts contain some substance responsible for their immunity to digestion?

In trying to answer the first two questions I had to expose the intestinal mucosa to gastric juice. I could either irrigate with gastric juice as Matthes did in acute experiments, or I could remove the alkaline bile and pancreatic juices so that the gastric juice would not be neutralized on arrival in the bowel.

### ACUTE EXPERIMENTS

Since I was much helped by Matthes' work, I will here review it. He made Thiry-Vella fistulas, isolating a loop of intestine, sewing both its ends into the abdominal wound and then restoring continuity in the remainder of the intestine.

After the wounds had healed he anesthetized the dog and irrigated the loop with artificial gastric juice.

After several hours of this the animals were sacrificed and the irrigated intestine was removed, and the mucosa was studied histologically. The following fluids were used by Matthes to irrigate the intestine.

A 0.57 per cent solution of HCl mixed with a peptone-free preparation of pepsin.

A 0.21 per cent solution of HCl with the same amount of pepsin.

A natural gastric juice prepared by the auto-digestion of hog's stomach and containing 0.58 per cent HCl.

A control was run each time with HCl of the same strength without pepsin. Irrigation with the first strongly acid fluid resulted in a few minutes in a marked degree of destruction of the mucosa, extending even into the deeper layers. Control experiments with HCl of the same concentration showed destruction of the villi, but practically no change in the deeper layers of the mucosa.

Irrigation with the second more weakly acid fluid caused destruction of only the tips of the villi. An HCl solution of the same strength produced about the same effect. Strange to say, the natural, highly acid gastric juice failed to produce any noteworthy change in the mucosa, and this despite the fact that it proved to be more active *in vitro* than was the first fluid used. Matthes concluded that the failure of the gastric juice to act as did the artificial one was due to the presence of large quantities of peptone, which formed loose compounds with the hydrochloric acid, compounds which interfered with its escharotic action. Actually, it is possible to demonstrate that such a combination of the HCl and peptones takes place.

I found that a hydrochloric acid solution of which 10 cc. was neutralized by 14.2 cc. of N/10 NaOH could be charged with an equal portion of saturated peptone solution to such a degree that in order to neutralize 20 cc. of the mixture only 10.0 cc. of N/10 NaOH was necessary. Congo red was used as an indicator. When phenolphthalein was used as an indicator, 15.2 cc. of N/10 NaOH was necessary to neutralize the 20 cc. This indicated that a combination had taken place between the amino groups of the peptone and the HCl indicator. Since the congo red does not react with organic acids and therefore also not with the acid groups of the peptone, in using it as an indicator signs of a reduction in the acid content were obtained. The phenolphthalein, on the other hand, appears to react with the amino acid groups, and for that reason, in using it, an increase in the acid titre was noted.

One can therefore not entirely dismiss the possibility that this combination of the HCl plays the role ascribed to it by Matthes. Nevertheless, it appears probable to me that another factor could also play a role. It is well known that peptone has a marked inhibiting effect on the digestion of pepsin *in vitro*, and it does not seem that the cause for this is its ability to bind HCl. It may be probable that this inhibiting property contributed to the results obtained by Matthes.

In most of Matthes' experiments, the loop of intestine used was near the ileocecal sphincter. In one case a jejunal loop was used which was 180 cm. from the ileocecal sphincter. In this experiment, which was carried out with a "natural" gastric juice containing 0.58 per cent HCl, Matthes found almost no change in

the mucosa, but when he performed a similar experiment with a more distally located intestinal loop, he found a marked hyperemia and multiple capillary hemorrhages.

From this work Matthes concluded that the more distal portions of the intestine are more sensitive to the effects of gastric juice than are the more proximal portions, which are frequently exposed to the gastric juice and which, perhaps as a result, are more accustomed to it.

This conclusion was open to criticism since the differences observed were slight. Matthes did, however, show clearly that pepsin solutions with approximately the same HCl content as that of gastric juice will destroy the mucosa in the distal portions of the small intestine.

I decided to repeat Matthes' experiments in somewhat modified form. My object was in acute experiments, to expose the upper portions of the intestine to the action of the gastric juice. To get rid of the neutralizing and diluting bile and pancreatic juice, I ligated the two ducts. Since it was important to expose the upper portions of the duodenum to the action of the gastric juice, I passed a cannula through the stomach and the pylorus. I used natural gastric juice obtained from Pavlov dogs. The free acidity of this juice varied usually between 0.51 and 0.54 per cent. The acidity and digestive power of the juice used was titrated in every experiment. The animals were kept under the influence of morphine and atropine. Whenever necessary some chloroform was given. The animals were quickly sacrificed after the irrigation.

#### IRRIGATION EXPERIMENT I

Under morphin atropin anesthesia the common bile and pancreatic ducts were ligated and a catheter was passed through the wall of the stomach, through the pylorus and into the duodenum. Some 15 cm. distal to the duodeno-jejunal juncture the bowel was cut across; the distal end was closed and the proximal end was cannulated.

The bowel was washed out first with salt solution at 37° C. Eight hundred cubic centimeters of dog's gastric juice was run through at the rate of one liter per hour. The experiment lasted *one hour and twenty minutes*.

Results: Necropsy showed the gastric mucosa normal, but marked damage had been done to the duodenal mucosa. The villi were almost gone and changes were present in the glandular epithelium. The epithelium was separated from the membrana propria; the nuclei and cells were shrunken; the connective tissue interstitial spaces were broader than normal, markedly infiltrated with small cells, and full of numerous hemorrhages. The changes were most marked at the apices of the mucosal folds and less marked in the depths. The disturbance began exactly at the dividing line between the gastric and the intestinal mucosae.

#### EXPERIMENT II

The same type of operation was performed but the catheter was placed 3 cm. lower in duodenum than in the previous experiment. Duration, *three hours*.

Results: Surrounding the head of the catheter was a blackish necrotic area. Distal to it the mucosa was

black, and apparently burnt. Proximal to the head of the catheter there was little change from normal.

### EXPERIMENT III

The common bile and pancreatic ducts were tied; then the stomach was cut across and the fundus closed off. The pyloric half was closed at the top and a fenestrated catheter was then led into it through the pylorus into the duodenum so that the acid could attack both stomach and duodenum.

Gastric juice containing 0.53 per cent hydrochloric acid was run through for *two hours and ten minutes*. Necropsy showed a normal gastric mucosa, but the duodenal mucosa showed marked changes distal to the pylorus. The villi were largely destroyed and much of the mucosa was gone.

### EXPERIMENT IV

The same arrangement was used as in experiment III except that the cannula extended down 40 cm. as far as the duodeno-jejunal junction. A portion of the intestine was cut off every twenty minutes and studied. The experiment lasted *one hour and twenty minutes*.

The gastric mucosa again was normal, but just below the pylorus the duodenal mucosa was markedly injured.

### EXPERIMENT V

Same arrangement as in experiment IV, but the common and pancreatic ducts were not ligated. Experiment ran for *two hours*.

Results: There were small areas of necrosis in the stomach corresponding to the holes in the catheter. The duodenal mucosa was badly injured all over.

### EXPERIMENT VI

The stomach was divided in the middle into two parts by a mattress suture. Otherwise the technic was the same as in experiment 4. Gastric juice was run in for *two hours*. The gastric mucosa was normal and the duodenal was badly injured.

### EXPERIMENT VII

The two parts of the stomach were divided by a clamp. Interestingly, through a misunderstanding with the helper in the laboratory, *the animal had been given food* and some of this was left in the pyloric portion. Otherwise the experiment was like number 6. Nine hundred grams of gastric juice were run in for *four hours*. At necropsy the gastric mucosa was practically normal except for a few areas of necrosis and the intestinal mucosa showed changes (milder than in experiments I and III.)

### EXPERIMENT VIII

The arrangement was the same as in experiment 7, with the difference that 500 gm. of 0.5 per cent hydrochloric acid was used. The experiment ran *two hours and thirty minutes*. At necropsy the gastric mucosa was normal. There was much less than the usual injury done to the intestinal mucosa, only the tips of the villi being injured. (If the conditions were exactly the same as in experiment 7, then one would have to explain the lessened injury either to the presence of food or to the use of pure hydrochloric acid.)

In all of these experiments, the intestinal mucosa which was exposed to gastric juice showed changes which were not of uniform intensity in all parts of

the irrigated regions. They were most marked in experiment II, in which the irrigation was carried out for three hours. In the most severely injured regions there was digestion down to the muscularis mucosae. The next most marked changes were observed in experiments I and III, where there was widespread destruction of the villi and in most places destruction of the glandular layer. In experiments IV (1 hour, 20 minutes) and V (2 hours) the changes were milder.

Less injured was the mucosa in the irrigated portions of the intestine, when the experiment was carried out with only hydrochloric acid. The changes then were limited to scattered areas of maceration of the villi. In the deeper layers of the mucosa no changes were observed. It should be pointed out that the intestinal mucosa when in contact with acid gastric juice always secretes a large amount of mucus and intestinal juice. In this way it protects itself to some extent.

In order to determine how rapidly dead intestinal mucosa is destroyed by gastric juice, a portion of the jejunum of the dog used in experiment VIII was cut out, tied off at one end, filled with gastric juice, and then tied off at the other end. Following this the segment was placed in a thermostat at 38° C. A *half hour later* the tissues were fixed. Macroscopically no change could be seen, but microscopically there was a destruction of the villi. In some areas they were all destroyed, whereas in some areas there was only some erosion of the tips of the villi.

In experiments from I to VI the changes observed varied, as one would expect, with the severity of the insult from the gastric juice, but in experiment VII I was surprised to find, after *four hours* of irrigation, changes which were milder than those seen in experiments I and III. The only difference in the conditions of this experiment and the preceding ones was that the animal had eaten a small quantity of meat one hour prior to the experiment. If this was actually the cause of the difference in the results, and if they were not the result of some other factor, one might offer the following explanations:

(1) The ingestion of food set some defensive mechanism into action.

(2) Peptones and other protein products of the meal inhibited the action of the gastric juice. However, since the quantity of meat was very small and the intestine was washed out with salt solution, and the quantity of gastric juice used was one liter, I disregarded this hypothesis I favor the first possibility as a result of further reasons which led to hypothesis 3.

(3) Peptones might be absorbed by the intestinal mucosa and stored there where they could act as a protection against the action of gastric juice.

Such an explanation fits well with the theory of reversible ferment processes.

### EXPERIMENT IX

The stomach and bowel were first irrigated with 500 grams of a saturated solution of Witte's peptone. This fluid, in the course of a half hour, was passed through the digestive tract. Then the stomach and bowel were washed out with physiologic sodium chloride solution until the fluid no longer gave the biuret test for protein. After this the irrigation was carried out with 500 grams of gastric juice for *two hours*. The HCl

content was 0.42 per cent, lower than that usually employed.

Results: The stomach was normal. The duodenum showed very little injury. There were a few punctate hemorrhages. Only the tops of the villi were eroded. The changes were decidedly less marked than in experiments V and VI, which also lasted two hours. (Apparently then, the entrance of peptone into the mucosa protected it.)

### EXPERIMENT X

The arrangement was as in experiment IX only the peptone was run into the bowel through a cannula.

I first irrigated the intestine with 500 cc. of concentrated Witte's peptone. This was warmed and passed through the gut again and again for one hour, during which time 400 cc. was absorbed. I then irrigated the intestine with a sodium chloride solution, and finally with natural gastric juice with 0.54 per cent free HCl (higher than in the previous experiment.)

Results: At the end of two hours, the gastric mucosa was uninjured. There was considerable injury for a short stretch just below the pylorus, but below that there was only a mild desquamation of the peaks of the villi.

My impression from these experiments was that the peptone which is absorbed by the intestinal mucosa protects it against the effects of gastric juice. In experiment X there was much neutralization of the acid, the concentration dropping from 0.54 to 0.19 per cent.

In experiments I and V the damage was about equally marked in all parts of the irrigated intestine. It was milder in experiments II and III, and there it

was not observed in the region near the pylorus. In these experiments the unequal damage may, however, have been accidental. In experiment IV the damage was marked immediately beyond the pylorus but milder further down. In experiments VI, VII and IX, the damage was definitely slighter in the upper duodenum than further down, and the conditions of the experiment could not be held responsible for this. I feel therefore that the proximal parts of the duodenum possess a greater resistance to the gastric juice than do the lower parts.

This may be due to eddies in the fluid. I doubt if my experiments show clearly that the upper portion of the duodenum is better able to withstand the gastric juice than the lower portions are. There is no difference either between the resistance of the upper jejunum and the duodenum. The natural gastric juice causes more marked destruction in the intestinal mucosa than does hydrochloric acid of the same degree of acidity.

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## Treatment

According to Dr. T. D. Spies (Science News Letter, June 1, 1940) patients with encephalitis have been helped greatly within a few minutes after the injection of doses of Vitamin B<sub>12</sub>. Tremor and rigidity decreased.

In the *Journal of the A. M. A.* for May 25, 1940, P. L. Davis reports that uniformly good results were obtained in the treatment of fourteen patients with recurrent herpes or herpetic fever with smallpox vaccine. Previous reports have also been encouraging.

In a paper by Harsh and Donovan (*J. A. M. A.*, 114:1859, 1940) it is reported that in a series of forty patients with several forms of allergic disease the results of treatment with potassium chloride were negative or questionable in all but one case. Incidentally, in these patients no significant alteration could be found in the amounts of serum sodium and potassium.

In *Science News Letter* for February 24, 1940, page 121, it is reported that Dr. Floyd DeEds of the Stanford University Medical School has found a chemical, phenothiazine, related to sulfanilamide, which is highly effective in the dislodgement from the bowels of livestock of several species of parasitic worms.

Dr. Fred R. Adams of New York, reported at a recent meeting of the Philadelphia Dental Society that

the injection of a hot solution of sulfanilamide directly into a dental abscess usually kills all the trouble-making germs and causes the abscess to disappear. It will be interesting now to see whether others can duplicate these results.

In the *Journal of the A. M. A.* for March 9, 1940, Drs. Wright and Brady report excellent results from the use of gentian violet in the treatment of infestation with pinworms. They treated 224 persons. Obviously the treatment had to be applied to all infested members of a family at the same time so that they wouldn't reinfest each other.

The dosage of the drug for adults was two 32 mg. tablets three times a day before meals, and for children the dose was 10 mg. a day for each year of apparent age. This amount should be given in three doses during the day. Treatment was kept up for ten days, and then swabs were taken from around the anus to see if the results were satisfactory. The pills were enteric coated. This gentian violet treatment was found to be superior to all others tested.

In the Archives of Dermatology and Syphilology for March, 1940, Turell, Buda and Marino report that the results of tattooing the perianal skin with mercury sulfide for pruritus ani have so far been encouraging.



## Current Comment

In the *Acta medica Scandinavica* for December 19, 1939, A. W. F. Jenner reports on the fate of 181 patients with pernicious anemia. He found that gastric carcinoma developed in eight. From statistical studies Jenner concluded that the expectancy of gastric cancer among 181 persons with the particular age and sex distribution should have been less than 0.3. He felt, therefore, that the incidence of cancer in this group was higher than one would normally expect, and this may be due to the presence of the atrophic gastritis.

In the *Archives of Internal Medicine* for April, 1940, Carl H. Greene and Elliston Farrell have reviewed the papers on the liver and biliary tract published in 1939.

In the January, 1940, number of the *American Journal of the Medical Sciences*, Sodeman reviews the recent literature on cardiospasm or achalasia of the esophagus. Probably the best method of treatment used today is dilatation of the cardia by the water-filled bag such as is used at the Mayo Clinic. This dilator is passed down over a thread anchored in the bowel and then pulled taut. Out of 804 patients so treated, 475 were apparently cured and 105 somewhat relieved. Hurst uses a mercury weighted bougie passed under fluoroscopic control. A few writers have reported good results from sympathectomy.

### GASTRO-INTESTINAL ULCERS AND CEREBRAL LESIONS

In the *Yale Journal of Biology and Medicine* for October, 1938, Oppen and Zimmerman studied the histories and postmortem findings in twenty-two cases in which a lesion of the brain was associated with ulceration or erosion or malacia in stomach or duodenum.

The lesions of the brain were located in the nuclei of the interbrain in sixteen instances, in the midbrain in two instances, and in three instances there was diffuse cerebral, chiefly cortical, involvement.

Obviously, more needs to be learned yet about the relation between injuries to the brain and ulcers of the stomach and duodenum.

### THE EFFECTS OF ANESTHETICS ON THE EMPTYING OF THE STOMACH

In the *Journal of Pharmacology and Experimental Therapeutics* for May, 1938, Sleeth and Van Liere

studied the changes in gastric emptying time in animals after the giving of an anesthetic. Chloroform delayed emptying by 64 per cent, ether by 40 per cent, nitrous oxide by 15 per cent, ethylene, cyclopropane and divinyl oxide each by about 7 per cent.

Enthusiasts in the removal of focal infections may be interested to note in an article by C. H. Brown in the April number of the *American Journal of the Medical Sciences* that 63 per cent of a group of psychotic patients who had definite foci of infection did not show any signs of arthritis, which indicates that besides the infection there must often be some factor of susceptibility or perhaps a hereditary tendency to arthritis or other disease.

### THE IMMEDIATE FEEDING OF THE PATIENT AFTER HEMATEMESIS AND MELENA

After a year's trial, J. D. Herlihy reported in the *Medical Journal of Australia* for December 10, 1938, that a combination of the features of the Meulengracht and the Sippy methods worked well in cases of bleeding ulcer. All patients received from 2,500 to 3,500 calories daily and a total fluid intake of at least 2,500 cc. They were allowed water or dextrose solution between meals, also milk sometimes flavored with malt preparations. Alkaline powders and belladonna were given only when this was thought necessary. Vitamins were given.

### HELP IN THE DIAGNOSIS OF INTRA-ABDOMINAL HEMORRHAGE

When a woman comes into the hospital with signs of something seriously wrong in the lower half of the abdomen, and the story of an acute episode a few days before which may well have been the rupture of an extrauterine pregnancy, the physician will welcome any help that he can get toward the making of the diagnosis.

In the *Journal of the American Medical Association* for October 16, 1937, page 1245, Dr. John Fallon of Worcester, Massachusetts, commented on the fact that he and his colleague, Dr. J. J. Dumphy, have found that in two out of three of these cases, if a hemorrhage has occurred, there will be an increase in the serum bilirubin.

## Editorials

### SHOULD ENEMAS BE BANNED?

**M**ANY physicians today strongly interdict the use of enemas by their patients, but just why they do this is not clear. So far we have not been able to learn from the literature or to get through personal communication any explanation for this prohibition. A few physicians have expressed a fear that occasionally the enema-taker will scratch the posterior wall of the rectum with the enema tip, but this, of course, can

easily be avoided by reminding the patient that the anal canal points backward and that the tip should be introduced pointing somewhat forward as well as upward. Some physicians seem to fear that the colon will be stretched out of shape, but if the enema consists of only 1 liter of water, it is hard to conceive how any such harm could be done.

Evidence has been brought forward from experiments on dogs to indicate that irritant enemas fre-



quently repeated can produce slight changes in the mucosa of the colon, but against this there is the evidence gained at thousands of necropsies and during thousands of sigmoidoscopic studies indicating that enemas can be taken daily for years without producing any sign of injury.

There are reasons for believing that the real objection of physicians to the taking of enemas by their patients arises in their dislike of a type of woman who is always fussing with her bowel, complaining about discomfort in it, and perhaps taking a couple of enemas a day. The physician fears, perhaps subconsciously, that the patient before him will develop an enema-habit and will become a "colono-centric" psychopath. Nowadays many patients have become so inoculated with this fear that they will refuse to take enemas when advised to do so. One way of combating this fear is to point out to the patient that he or she has the constipation habit, and *something* has to be done every day or two to empty the bowel. Perhaps the enema habit is no worse than the constipation habit. Actually only a mildly insane person who believes that intestinal auto-intoxication is destroying his brain, or a person who suffers much misery from a hypersensitive painful and gas filled colon is ever going to take more than one enema a day.

Unfortunately, we of the medical profession have always tended to follow fads. In the time of Molière the great fad was the giving of medicated enemas. Before and after that the fad was to give powerful purgatives. Later it became fashionable to give mild laxatives. Today most of us deny to our constipated patients every mode of treatment except a rough diet and some form of gummy substance which imbibes water and makes a bulky stool. To most physicians the giving of laxatives or enemas is outmoded and anathema. Just why this should be is hard to say. When a little old lady says that for forty years she has regulated her bowels perfectly each day with an enema, a little cascara or a rectal suppository, it would seem as if the physician should give her his blessing and tell her to continue as she has always done.

Usually physicians should suspect that they have stopped thinking when they get to treating all their patients the same way. At first sight it would seem more salutary to relieve constipation with a diet rather than with a laxative, but the more one talks this over with the physiologists, the less sure one is that the "Nature way" *must be* better. One is more inclined to ask *is it* better? Furthermore, it is hard to see how a fig or a prune or a psyllium seed is any more a "Nature remedy" than is a senna leaf or a bit of cascara bark or a quart of water.

All that one learns from the history of medicine suggests that some day the present fad will pass and then perhaps it will be recognized that a bulk-producing diet does not work well for every person, and often when it does work well it later ceases to do so. The colon becomes so accustomed to the gummy substance used that then no amount of it will produce laxation and a bulky stool.

In many cases of constipation the most logical method of emptying the colon would seem to be with an enema. As every gastro-enterologist knows, there is practically no such thing as a small bowel consti-

pation. In almost every case the stagnation is in the rectum or in the distal third of the colon. Does it not seem foolish then to disturb the functions of 12 feet of small bowel and perhaps hamper digestion in it when all that is needed is the cleaning out of the last foot of colon? Does it not seem more logical to remove the fecal material from the lower end of the gut with an enema?

If, then, one is to prescribe enemas, what fluid should be used? The most logical material to be used, especially in persons with an irritable, overly sensitive colon, would seem to be a physiologic solution of sodium chloride. There is all the more reason for this view now that Clarence Dennis has reported in the April, 1940, number of the "American Journal of Physiology" that distilled water produces temporary injury to the mucosa of the bowel, or at least, in the lower part of the ileum. This injury was shown by changes in the reaction of the mucosa to sulfate ions, and by changes in the histologic picture.

It is hard to see how physiologic saline solution can do any harm to the intestinal mucosa any more than one can see how tears can do harm to the cornea of the eye. It would seem then as if the *routine* enema used in hospitals and clinics where many patients come with a sensitive bowel should consist not of soapsuds but of physiologic saline solution. Because use of the nonirritating fluid cuts down on the amount of spasm in the bowel, it is often much easier to get an enema of physiologic saline solution into the colon than it is to run in the same amount of irritating soapsuds: there is much less spasm and pain. Even an enema of plain water is hard to give to a person with a highly sensitive colon, because of the spasm produced. Furthermore, and this is important, it is much easier to get physiologic saline solution out of the colon than it is to get water out. Many persons with a highly sensitive colon will not use enemas because they cannot get plain water or soapy fluid out once they have gotten it in. There is too much spasm.

Many patients object to the taking of enemas also because, the way they do it, it takes too much time. They have been taught to lie on the floor, to roll from side to side or to get into the knee-chest position, and they have been told to retain the water for some time before trying to expel it. None of these injunctions seem logical, and practically, they all are unnecessary. It should be obvious that if a quart of water is run in at the anus it must go well up into the colon no matter what position the recipient assumes.

Actually an enema can be taken satisfactorily while the patient is seated on the toilet, and the water should be let out as soon as it is run in. About a tablespoonful of salt should be added to the quart of water. A long rectal tube should never be used: it will only coil up in the bowel. Enema tips should be made some day with a little shoulder which will help to keep the water from coming back through the anus. When a cramp comes in the colon the rubber tube should be pinched shut for a few seconds until the muscle relaxes.

We recently saw two women, one of whom had taken at least one enema a day for ten years and the other had taken several a day for seventeen years. The first brought with her a pile of films of the colon made at

interests during the ten years. They showed no increase in either the duration or the length of the illness, and sigmoidoscopic examination showed a normal mucosa. The other woman also had a colon which appeared to be normal in every way. It would seem as if these women had done everything possible to prove that enemas can be taken without doing harm to the bowel.

Actually, in many cases enemas solve satisfactorily the problem of the constipated person. In some cases they do not work well, and then, of course, other measures will have to be tried. In other cases, diet or mild laxatives work so well that it is hard to see why one should ask the patient to change to the use of enemas. W. C. A.

### NEUROTROPIC VIRUSES INHABITING THE BOWEL

**P**ATIENTS commonly ascribe their feelings of fatigue and ill-health to disturbances in the bowel, and often their story does suggest that some change has taken place in the flora of the intestine. Perhaps there appears to have been some infection with an unknown pathogenic organism or virus, but in most cases, even when the physician works in a university hospital and has at his side to help him an expert bacteriologist and a research laboratory, he is unable to find what the disturbing organism or virus is.

Decidedly interesting and possibly of significance to those of us who practice medicine is the report by Peter Olitsky in the February, 1940, number of the "Proceedings of the Society for Experimental Biology and Medicine," to the effect that normal mice and also those infected with a type of encephalomyelitis carry in their intestinal contents a virus which, on transfer into the brain of normal mice, will induce the characteristic signs of spontaneously developing encephalomyelitis. Immuno-logic studies indicate the identity of the virus that produces the spontaneous encephalomyelitis with that which is obtained from the intestines of normal mice.

This virus shows up in the bowel shortly after the newborn mice are weaned, and it tends to disappear as they grow older. Curiously, the agent is not found in the brain of normal mice even when the intestine is full of it. It has not been possible to demonstrate the virus in the intestines of the fetuses of infected mothers.

Interest aside, it has recently been shown that the virus of poliomyelitis of children can also be recovered from the stools.

It is interesting also that the filtrable virus which probably causes the common cold is also present in stool, on the post-infectious stage, in association with a severe post-infectious asthmatic disturbance and perhaps a little diarrhea. This would mean a rather high level of excretion of it.

Recently we saw a man who, for five years, suffered from an illness which he called "flu." This condition was found to be full-blown poliomyelitis, and he was cured by the transfer of spinal fluid. The great question was, was the diarrhea due to the effects of the disease or the spinal fluid? There is a story about the man's cure was that half of the time

most of the bowels. But the virus affects neither the nerves, directly, nor the muscles, so that some of the "flu" was something else? W. C. A.

### THE HYPOTHALAMIC NUCLEI OF THE BRAIN AND THEIR INFLUENCE ON THE DIGESTIVE TRACT

**I**N volume XX of the "Hesiodic publications of the Association for Research in Nervous and Mental Disease," "The Hypothalamus and Central Nuclei of Autonomic Function," Williams and Williams, Editor, Paul Stebbins of New York University, has translated a chapter on the regulation of gastrointestinal functions from the part of the brain. The chapter is a review that stimulates, or, if one is a critic, parts of the brain can have a profound influence on the digestive tract. As long ago as 1842, David L. Blandford, from his vast experience at the autopsy table, commented on the fact that infectious lesions involving the base of the brain are commonly associated with gastric disturbances, occasionally with gastric hemorrhages, and often with spasm or post-mortem perforation of the stomach or duodenum. It was not until 1914 that disease in the posterior fossa was demonstrated to cause such gastric ulceration.

From his review of the recent literature Stebbins concluded that adequate stimulation of the hypothalamus is followed by inhibition of peristalsis and diminished muscle tone in the stomach and small bowel, also by an increase in the amount of secretion in the gastric juice, and a tendency to a decrease in the rate of flow of this juice.

There is now strong support for the view that there exists a center in the hypothalamus which regulates gastrointestinal activity through the sympathetic nervous system. Some observers have reported a greater flow and an increase in acidity of the gastric juice following stimulation of the anterior part of the hypothalamus.

Injury to the hypothalamus region, results in a third of the experiments, is associated with emaciation, changes and spasms in the stomach, and changes in blood sugar, and lesions in the hypothalamus are followed by gastrointestinal changes more or less frequently than are lesions elsewhere in the central nervous system. Other parts of the brain, such as the pons, have something to do with producing gastric secretions, and the medulla, the pons and the frontal lobe.

There appears to be a close relationship between the gastrointestinal lesions produced by injury to the hypothalamus, lesions of the posterior nucleus, by removal of both lateral planes, and by the posterior plane alone, which are produced by lesions of the hypothalamus, and lesions of the pons. No correlation has yet been shown between the lesions of the pons and the

### WORLD CHAMPIONSHIP SHOULD BE INSTRUCTIONS OF GAMES, ETC.

It is one of the facts that there is a tendency to suggest that the world championship should be a contest of instruction, it would be interesting to know if a contest between a champion and a beginner in the art of instruction should be held. W. C. A.

## Abstracts of Current Literature

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KOKAS, E. VON: *Vergleichend-physiologische Untersuchungen über die Bewegung der Darmzotten*. Arb. ungarisch. biol. Forschungsinstit., 10:275-278, 1938.

Treatment of the duodenum of rabbits and rats with diluted HCl causes increased movements of the muscles in the mucous membrane. Extracts made from the mucous membrane of rabbit's intestine with HCl have similar effects both on the finger-like and the flat filaments.—Courtesy of Biol. Abst.

POPESCO, SIMICI ET: *Action de l'urée sur la Musculature Gastro-intestinale*. Bul. de l'Acad. de Méd. Bucarez, t. IX, p. 85-92, 1940.

Researches made on dogs and cats have shown the authors that the urea may inhibit the gastric motility. As to what concerns the tonus of the digestive tract the action of this substance differs for every muscular layer. Urea produces hypertonus of the longitudinal musculature. Otherwise it produces a certain weakening of the circular musculature—I. Pavel.

SCHIFFRIN, M. J. AND NASSET, E. S.: *The Response of Jejunum and Ileum to Food and Enterocrinin*. Am. J. Physiol., 128(1):70-80, 1939.

Auto-transplants of jejunum and ileum in the belly wall of dogs were used for the production of succus entericus. In normally innervated fistulas of this type, feeding diminished both enzyme conc. and total production. This inhibition persisted in the jejunum for 6 or 7 hours and in the ileum for at least 8 hours. Section of the extrinsic nerves abolished the inhibition. This result is interpreted to mean that there is an antagonism between the action of the extrinsic nerves and the enterocrinin produced in the intact intestine during the process of digestion. The adm. of enterocrinin either intravenously or subcutaneously overcomes the normal inhibition and this effect is accentuated by denervation. The hormone injections bring about increased conc. and total production of the 4 enzymes present in succus entericus; chloride, pH and total CO<sub>2</sub> are not affected.—Courtesy of Biol. Abst.

NORTHUP, D. W. AND VAN LIERE, E. J.: *Intestinal Secretion During Anoxia*. Proc. Soc. Exp. Biol. and Med., 42(1):162-163, 1939.

The effect of anoxia was studied in intestinal secretion of dogs. 5 hours before the expt. they were fed a meal of cooked hamburger to encourage intestinal secretion. One animal served as a control and the other was subjected to anoxia. Peptone extract (prepared according to the method of Nasset and Pierce) was given intraven. 20 minutes later the animal was sacrificed. At a partial pressure of 0<sub>2</sub> of 80 mm. Hg (approx. altitude 18,000 ft.) no effect was noted on the amount of intestinal secretion. At 53 mm. Hg (28,000 ft.) there was a mild depression of the secretion, which was not statistically significant. This indicated a low energy requirement for intestinal secretion.—Courtesy of Biol. Abst.

KATZENELBOGEN, S., LOUCKS, R. B. AND GANTT, W. H.: *An Attempt to Condition Gastric Secretion to Histamin*. Am. J. Physiol., 128(1):10-12, 1939.

Using histamin as a type of drug producing an effect through peripheral instead of central action, the authors tried to condition gastric secretion produced by the injection of histamin in dogs with Pavlov pouches. Although a good unconditioned secretion was obtained, after as many as 75 injections at daily intervals in 3 dogs, there was no evidence of a conditions gastric secretion to the injection of normal saline. These expts. together with the authors' failure to condition adrenalin hyperglycemia are evidence for the necessity of a central excitatory state for the formation of the conditioned reflex.—Courtesy of Biol. Abst.

GRUBER, C. M., HAURY, V. G. AND DRAKE, M. E.: *Action of Apomorphine Hydrochloride on the Intact Intestine in Unanesthetized Dogs*. Proc. Soc. Exp. Biol. and Med., 42(1):193-197, 1939.

6 dogs with Thiry-Vella loops were given intravenously 0.02 mg. apomorphine hydrochloride per kg. and the activity of the intact gut studied. In 10 of the 22 experiments an unmistakable increase in tonus, which lasted over 38 minutes in some cases, was observed. In 5, a decrease in general tonus only was observed and in the remaining 7, the results were doubtful. The peristaltic contractions may be augmented by apomorphine especially when the general tonus is diminished. Borborygmi are commonly noted following the intrave. injection of apomorphine.—Courtesy of Biol. Abst.

FOGELSON, S. J. AND BACHRACH, W. H.: *Response of Brunner's Glands to Secretin*. Am. J. Physiol., 128(1):121-123, 1939.

Intraven. injection of secretin is followed by the secretion of a viscid juice from the Brunner's gland area of the duodenum, but proof is still lacking that this secretion is entirely independent of the increased duodenal motility accompanying it.—Courtesy of Biol. Abst.

BUSSABARGER, R. A.: *An Improved Method for the Study of Intestinal Function*. Proc. Soc. Exp. Biol. and Med., 42(1):50-51, 1939.

A modification of the classical Thiry-Vella operation is described. The resultant prep. possesses a perfectly functioning pouch retained subcut. This enables not only bolus and balloon studies to be conducted, but also permits a direct visual observation of the peristaltic waves through the thin overlying skin.—Courtesy of Biol. Abst.

BURSTEIN, C. L.: *Effect of Spinal Anesthesia on Intestinal Activity*. Proc. Soc. Exp. Biol. and Med., 42(1):291-293, 1939.

The effect of spinal anesthesia on intestinal activity was studied in unmedicated dogs with Thiry-Vella fistulas of the jejunum and ileum. Spinal anesthesia caused constant increase of intestinal contractions.—Courtesy of Biol. Abst.

BARNES, R. H., MILLER, E. S. AND BURR, G. O.: *In Vitro Incorporation of Fatty Acids in Phospholipids of Intestinal Mucosa. Proc. Soc. Exp. Biol. and Med.*, 42(1): 45-47, 1939.

Normal, post-absorptive, rat intestines after feeding the methyl esters of conjugated corn oil (a labeled fat) were incubated at room temperature. Labeled fatty acids were incorporated in the mucosal phospholipids. There was a simultaneous destruction of total mucosal phospholipids.—Courtesy of Biol. Abst.

BALL, GORDON H.: *The pH of the Digestive Tract in the Living Albino Rat as Determined by the Capillary Glass Electrode. Am. J. Physiol.*, 128(1):175-178, 1939.

These readings show that the wall of the duodenum is rather consistently acid (avg. pH 6.48), that the ileal and cecal walls are usually alkaline (avg. pH 7.32 and 7.28), while that of the colon approaches neutrality (avg. pH 7.15).—Courtesy of Biol. Abst.

DRASTEDT, L. R., DONOVAN, P. B., CLARK, D. E., GOODPASTURE, W. C. AND VERMEULEN, C.: *The Relation of Lipocic to the Blood and Liver Lipids of Deapancreatized Dogs. Am. J. Physiol.*, 127(4):755-760, 1939.

The blood lipids of deapancreatized dogs fed balanced diets increased about 25% the first week after operation and then decreased gradually to a level about half the normal in 6 weeks. At this time the livers were markedly infiltrated with fat. The oral adm. of lipocic produced a prompt elevation of the depressed blood lipid level and a more gradual disappearance of the liver fat.—Courtesy of Biol. Abst.

GREENBAUM, F. R.: *Allantoin, a Possible Leucocytosis Producing Factor. Medical Record*, April 17, 1940.

Greenbaum is of the opinion that allantoin possesses leucocytic stimulating properties because he found that when this substance was injected, especially intramuscularly, a definite response in the increase of neutrophilic leucocytes occurred both in rabbits and in dogs, the response being best when only one injection was made. It is also found that the drug, when given orally, produced a leucocytic response though not as marked as when given intravenously or intramuscularly. He believes that this effect of allantoin opens up the possibility that this substance exerts its healing action due in part to a possible local leucocytosis at the site of the wound or the osteomyelitis.—Exp. Physiology.

ANTOINE, E.: *Les Infections Bucco-gingivales d'origine Intestinale. Syndromes Entéro-buccal et Entéro-pharyngien. La Pyorrhée d'origine Intestinale. Arch. des Mal. de l'app. dig. et des Mal. de la Nutrit.*, t. 29, pp. 588-615, 1939.

In those patients who complained of intestinal diseases we often find gingivitis, pyorrhoea, coated tongue and chronic pharyngitis. Hémo-culture of the gums or by scraping at the basis of the tongue, or from the border of the gums, have shown the author that there were the normal microbes of the intestine: collibacil, enterococcus, staphylococcus sometimes associated with streptococcus.

The infectious focus of the gums and dental parts seemed to be secondary to the intestinal focus.—I. Pavel.

BECKS, H. AND WAINWRIGHT, W. W.: *Human Saliva. VII. A Study of Rate of Flow of Resting Saliva, by H. Beck. VIII. A Study of Rate of Flow of Activated Saliva, by W. W. Wainwright. IX. The Effect of Activation on Salivary Flow, by H. Beck and W. W. Wainwright. J. Dental Res.*, 18(5):431-456, 2 figs., 1939.

This symposium of 3 reports on active and resting saliva presents a critical study of rate of flow under definite conditions. Since mixed human saliva is a typical secretory and excretory product, fluctuations in rate of flow

cause changes in composition which may provide an explanation for some of the great discrepancies noted in published reports of investigations between salivary composition and oral disease. Investigations extending over a period of 2 years show that fluctuations in the rate of flow is less in the saliva of persons with lower rate of flow, 5.4 cc. per hour, than in those with higher rates, 24.6 cc. per hour, when calculated over a longer period of time. In a 5 day period the difference is hardly noticeable on a % basis, but on a 2½ hour continuous collection basis, the % fluctuation is greater, the lower the initial rate of flow during the resting stage. Activation with paraffin causes a greater fluctuation in the higher rate per hour group when figured on a cc. per hour basis, but the difference is slight on a % basis. A great variance is noted in individual response, and in the fluctuation in rate of flow when the saliva is activated 8 successive times for a period of 45 minutes. The subjects in both groups reach the same level of activation in a certain period of time whether the original rate is slow or fast in the resting stage, but the % increase is very marked.—Courtesy of Biol. Abst.

BUSCHKE, FRANZ AND CANTRIL, SIMEON T.: *The Dentist and Cancer. Radiation Therapy Supplement, Staff J., Swedish Hosp., Seattle, Washington, No. 1, p. 48, Feb., 1940.*

The oral cavity belongs to the borderline fields of the gastro-enterologist and is of the greatest importance. The authors discuss cancer of this region. They stress the fact that leukoplakia is a frequent precursor of carcinoma. All the factors which might cause chronic irritation may also produce leukoplakia. Chronic irritation by tobacco in the form of smoking and chewing, electric current due to fillings of dissimilar metals are causes to produce leukoplakia. Carcinoma found in the oral cavity are of the squamous cell type, giant cell tumors of the jaw, adamantinoma, carcinomas of the maxillary sinus, and aberrant salivary gland tumors. The authors show excellent photographs of the different types of these tumors, and confront them with benign changes seen for instance after cautery.

Even if the article is especially directed to the dentist, the gastro-enterologist will be interested in this very important, however rarely discussed field.—Franz J. Lust.

RITVO, MAX AND McDONALD, EUGENE J.: *The Value of Nitrites in Cardiospasm (Achalasia of the Esophagus). Am. J. Roent. and Radium Therapy, Vol. XLIII, No. 4, April, 1940.*

Cardiospasm is an idiopathic stenosis of the lower portion of the esophagus with marked dilatation above the point of obstruction. The condition is believed to be due to a defective relaxation of the normal tonicity rather than a spasm and should more properly be termed achalasia of the esophagus.

The administration of amyl nitrite or nitroglycerine produces a disappearance of the stenosis of the esophagus in many cases of cardiospasm, permitting the passage of fluid and food into the stomach.

The abolition of the obstruction in those cases in which the drug is effective gives the patient relief from his distressing symptoms; it permits of accurate roentgen visualization of the esophagus and the remainder of the gastrointestinal tract; the passage of dilators may be facilitated and the dangers of traumatism or perforation during instrumentation lessened.

The effect of the drugs is of short duration; nevertheless these agents appear to have a definite though limited application in the treatment of cardiospasm.—Franz J. Lust.

LIEBER, M. M., STEWART, H. W. AND MORGAN, D. R.: *Adenosquamous Carcinoma of the Peripapillary Portion of the Duodenum. Arch. Surg.*, 40:988, 1940.

In their extensive reviews of peripapillary and suprapapillary carcinoma of the duodenum, the authors found

5 cases which were histologically adenosquamous or squamous in character. This paper reviews these 5 cases and an additional case of the authors which is described in extenso. Only 2 per cent of carcinoma in this region showed squamous cell characteristics. The clinical picture in these 6 cases was that of sudden onset of jaundice, with death occurring on the average 4 months after the onset of symptoms. At autopsy metastases were demonstrated in all cases.

The origin of the tumor found in the suprapapillary portion of the duodenum was evidently in the duodenal mucosa. However, in the cases found in the peripapillary region, the complicated structure of the tissues at the point where the common bile duct, as well as the pancreatic duct, join the duodenum makes it difficult to determine the source of the tumors. The possible genesis of squamous cell carcinoma in this region was discussed and it was considered that metaplasia, as a result of chronic irritation, was the most rational explanation.—Henry Doubilet.

BRULÉ, M., HILLEMANT, P., GILBERIN, E. ET COLLANDRY, L.: *L'ulcère de la Deuxième Portion du Duodenum*. Arch. des Mal. de l'app. dig. et de Mal. de la Nutrit., t. 29, pp. 846:855, 1939.

It is an exceptional localization of the duodenal ulcer. The D II ulcer is particularly frequent to the natives of Tunis. The authors found only 94 cases in medical literature. They stated that the D II duodenal ulcer may be symptomless or that it may cause recurring but rare attacks of dyspepsia. There are also cases with recurring icterus.

One case of D II ulcer was described. No characteristic symptoms were found. Only the X-ray method helped for positive diagnosis. Here too one can meet some diagnostic difficulties on account of diverticula of the duodenum.—I. Pavel.

MCPEAK, CLARENCE N.: *Benign Duodeno-colic Fistula*. Radiology, 34:3, 343-349, March, 1940.

Benign duodeno-colic fistula is a rare finding. The benign fistula is usually due to a perforation of a duodenal ulcer into the transverse colon and it may involve any part of the duodenum.

The diagnosis is not difficult if the colon is examined with a barium enema, but the fistula may not be demonstrated if the examination is limited to a barium meal.

The benign origin of the fistula may be suspected from its appearance on roentgen examination, but operation is necessary to exclude definitely the presence of a cancer.

Two cases are reported which have been proved by operation and also, in one instance, by postmortem examination to be due to a perforation of a duodenal ulcer into the transverse colon.—Franz J. Lust.

DOUB, H. P.: *The Differential Diagnosis of Pyloric and Prepyloric Ulceration*. Am. J. Roent. and Rad. Ther., 43:826-831, June, 1940.

Doub in an interesting article re-emphasizes that the differentiation between benign and malignant ulceration in the pylorus and prepylorus cannot always be accurately made by means of the roentgen examination alone. It is well known that carcinoma of the pylorus may simulate benign lesions clinically and may show a considerable amount of relief following the usual medical therapy. Mentions Holmes and Hampton's belief that any chronic indurated lesion occurring in the pyloric antrum within one inch of the pylorus but not involving it, should be considered malignant until proved to be benign. Jensen and Rivers are also quoted as to the extreme difficulty encountered in lesions of the pyloric ring to arrive at an accurate diagnosis even after all means at the disposal of the clinician are utilized. They estimate that in about 15

per cent of cases with pyloric lesions they are unable to be certain that the lesions are not malignant.

Doub studied 35 cases in which the final diagnosis was made by microscopical examination. Of these 24 were benign peptic ulcers, 16 of which were located in the prepylorus and 8 in the pyloric ring. There were 7 cases of carcinoma of the antrum, 3 with gastritis and 1 case of syphilis of the antrum.

Stressing the importance of determining the location of the ulcer, he observed the difficulty in a number of cases, to be certain whether the ulcer was in the prepylorus or in the pyloric ring. In benign ulceration the chief difficulty is due to spasm and in these cases there was difficulty in demonstrating a niche. In cases without the niche, he recommends progress examinations at intervals of a few weeks. Malignant gastric ulcers are usually large sized, often hazy and irregular in outline. Those occurring in the pyloric antrum have a higher percentage of malignant degeneration than those in other portions of the stomach.

The author discusses briefly, antrum gastritis and gastric syphilis, and emphasizes the importance of early diagnosis of lesions occurring in the pylorus and prepylorus.—Maurice Feldman.

LAW, W. ALEXANDER: *Perforated Jejunal Ulcer Following Partial Gastrectomy*. Brit. Med. J., 1:844-846, No. 4142, May 25, 1940.

Acute perforation following partial gastrectomy is a rare condition; only two such cases were found among the records of the London Hospital in the past ten years. During the same period there were 20 cases of perforation following gastrojejunostomy.

Two cases are recorded in detail, one of which had four hospital admissions. Both cases presented evidence of duodenal ulcer with high gastric acidities. The perforation occurred at a similar site in both cases, i.e. in the jejunum just distal of the line of anastomosis, one the posterior surface. From the results of these cases, a suggestion is made that if a partial gastrectomy must be done for a duodenal ulcer, it should be a high one and that a more radical or subtotal gastrectomy should be performed primarily.—Maurice Feldman.

MCPEAK, C. N.: *Syphilis of the Stomach with a Report of an Unusual Case*. Am. J. Roent. and Rad. Ther., 43:832-844, June, 1940.

McPeak notes the paucity of syphilitic involvement of the stomach found at autopsy and mentions the factors which account for this discrepancy. The microscopic examination is the least accurate of all of the methods of making the diagnosis. The gross pathology of the disease is much more typical than is the histopathological. Some authors demand that the *Treponema pallidum* be demonstrated in the tissue, but the author states that it is impossible to demonstrate the *Treponema pallidum* from other spirochetes on microscopic examination of tissues.

Clinically the history may either be that of ulcer or carcinoma. It is frequently mistaken for carcinoma. Vomiting is a frequent occurrence; hemorrhage occurs in about 50 per cent of cases; there may or may not be pain, which may or may not be associated with eating. There is usually an absence of HCl. In advanced cases the stomach may be markedly reduced in size; the lower end of the esophagus may become dilated, due to the diminished volume of the stomach.

In latent syphilis a smooth mucosa is seen according to Gutzeit and Teitge who conclude that the tendency in syphilis where any change in gastric mucosa occurs, is toward the atrophic state. Gummata are rarely if ever found in the stomach, but gummatoïd areas may sometimes be found which strongly suggests the nature of the pathology. The most common finding is the granulomatous thickening and induration of the wall of the stomach.

McPeak calls attention that at operation in carcinoma

one finds a more extensive involvement than the X-ray indicates, while in syphilis of the stomach there is a surprising paucity or complete absence of changes as determined by palpation. The common lesions of gastric syphilis is not a spherical prominence as in a tumor, gummatous or neoplastic, but is a flat infiltrate that leads to a plaque-like thickening of the gastric wall. When thin the infiltrate is easily overlooked; when thick its relative soft consistency and pliability distinguishes it from carcinoma.

Three varieties are noted: gastritis, ulcer, gummatous hyperplasia. The location given by Moore and Aurelius is as follows: prepyloric 70 per cent, medium or hour-glass 22 per cent and diffuse 8 per cent.

If an ulcer is present the niche will usually not penetrate beyond the normal limits of the gastric lumen as it does with benign gastric ulcer, but will be seen to involve the filling defect in a manner similar to that seen in an ulcerating carcinoma. If a tumor is palpated it usually will be much less prominent than the size of the filling defect would indicate. This latter observation is very important in differentiating between syphilis from carcinoma of the stomach. The absence of a palpable mass notwithstanding the presence of a gross and constant filling defect has been emphasized more than any other sign.

Following antiluetic therapy the lesion may be seen to disappear but at a later date the filling defect may reappear due to scar tissue. In many other cases and in all cases showing extensive involvement no change will be noted in the X-ray findings in spite of the clinical improvement.

McPeak reports an interesting case studied over a period of seven years in a male aged 62. The X-ray at first showed a smooth filling defect on the greater curvature of the stomach, which finally in latter examinations resulted in a markedly contracted stomach of a linitis plastica type. The condition was first diagnosed as carcinoma. A Hinton test revealed a strongly positive result. At autopsy the stomach size was greatly reduced. Microscopic study of the tissue showed scattered groups of lymphocytes and plasma cells, epithelial-like with giant cells were seen between the muscle fibers, findings consistent with syphilis.—Maurice Feldman.

WALTERS, W.: *The Surgical Treatment of Ulcerating Gastric Lesions. Am. J. Roent. and Ther.*, 43:810-825, June, 1940.

Walters expresses anew the fact that no patient should be placed on a medical regimen for what seems to be a benign lesion of the stomach or duodenum, without its first being ascertained by roentgenologic examination whether the lesion is in the stomach or duodenum. If it is on the stomach side, the possibility that the lesion may be malignant in spite of the fact that it does not appear so on the initial roentgenologic examination should be kept in mind. This also holds true in cases in which the lesion may seem to disappear roentgenologically, under a medical regimen. The author emphasizes the frequency of errors made in the interpretation between cases of obstruction of the pylorus and duodenum. Attention is also directed to the necessity of differentiating the benign gastric ulcer from the gastric ulcer with malignant changes. However, a roentgenologic report that a lesion is a gastric ulcer, does not exclude its being carcinomatous.

Walters discusses gastric polyps and points out that frequently malignant cells may be found in its periphery. The frequency of anemia in bleeding polyps is stressed.

The operability of gastric lesions and the types of operations are discussed. Mention is made of the low mortality in operative procedures for peptic ulcer. He points out that the operability of a gastric lesion cannot always be determined by the roentgenologist.—Maurice Feldman.

LAING, G. H.: *Clinical Consideration of the Stomach. Am. J. Roent. and Rad. Ther.*, 43:805-808, June, 1940.

Laing describes pylorospasm as a spastic contraction

of the thickened circular stomach muscle of the pyloric sphincter. He points out that our knowledge of the causes of pylorospasm is very limited, due to the complexity of the physiological control of the pylorus. The sympathetic component of the vegetative system is generally considered to be inhibitory to the pyloric sphincter, and the vagus motor in its action. However, the opposite effect may be obtained from either nerve, the tonus at the time appearing to be a determining factor. Variations in response seems to be characteristic of gastric nerves and this may help to understand the paradoxical effects one obtains with certain drugs at times. The author discusses both intrinsic and extrinsic factors in the causation of pylorospasm. The most common intrinsic cause is peptic ulcer, while extrinsic factors are due to a large number of conditions. Mention is made of the following conditions which may cause reflex spasm of the pylorus, namely, gall stones, appendicitis, renal calculi, pyelitis, diseases of the genitalia, allergic states, toxic states, endocrine disturbances, diseases of the central nervous system, lesions of the brain, and psychoneurosis.

Laing emphasizes that fact that fundamentally, it would appear that pylorospasm is the result of an automatic imbalance.—Maurice Feldman.

LUNDBAEK, K.: *On the Diagnosis of Gastritis. Acta Med. Scand.*, 101(4/6):575-505, 1939.

In cases where the customary methods of examination are not suggestive of this diagnosis, gastroscopy demonstrates the presence of gastritis. Negative gastroscopic findings may be taken to mean an absence of gastritis. It is suggested that the diagnosis "dyspepsia" be limited to cover gastroscopically negative cases. In gastroscopic gastritis, the symptomatology and ordinary findings in clinical tests are found to be most variable. "Dyspeptic" cases, the gastroscopically negative, show the same variability as to symptomatology and the ordinary tests as do the cases of gastritis. Positive X-ray findings often, but by no means invariably, are associated with gastroscopic gastritis. Negative X-ray findings mean nothing. Schindler's hypertrophic gastritis does not constitute any sharply defined clinical entity, but it is undoubtedly to be considered a more advanced stage of gastritis. Atrophic gastritis is associated most frequently with achylia, but normochylia may be present in such cases.—Courtesy of Biol. Abst.

CHONT, L. K.: *Primary Sarcoma of the Stomach. Radiology*, 34:714, June, 1940.

There are no characteristic symptoms and signs of gastric sarcoma to differentiate it from carcinoma. Hemorrhage with recovery and recurrence without marked anemia are suggestive observations. Chont believes that, roentgenologically, a flat tumor with smooth borders, pedunculated growth, isolated filling defect on the greater curvature with deep indentation or with a crater shadow in it, and tumors on the greater curvature side of the fundus, are suggestive of sarcoma. These tumors are radiosensitive. Large tumors may be rendered operable by preoperative radiation therapy. Three case reports are described in detail. One patient was three and one-half years old, and is believed to be the youngest individual with this lesion reported in the literature.—Robert Turell.

BENJAMIN, E. L. and CHRISTOPHER, F.: *Primary Lymphosarcoma of the Small Intestine. Am. J. Clin. Path.*, 10:408-413, June, 1940.

The authors report a case of primary lymphosarcoma of the ileum in a female aged 57 and demonstrate a roentgenogram of a markedly dilated bowel proximal to the obstruction. There were no characteristic symptoms. The patient complained mostly of loss of appetite, loss of weight, pains on left side of abdomen and recent vomiting.

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BINKLEY, J. S.: *Aspiration Biopsy of Tumors of the Liver. A report of nineteen cases. Am. J. Cancer, 36(2): 193-200, 4 figs., 1939.*

Sufficient material was obtained by aspiration biopsy in this series to establish a diagnosis in 73.6% of the cases. Follow-up records of the clinical course supported the histologic diagnosis. Aspiration biopsy of tumors of the liver was not associated with significant complications in the hands of 10 different clinicians who had used the method upon one or more occasions.—Courtesy of Biol. Abst.

ANDRUS, W. DE W. AND MOORE, R. A.: *Lipid Amino Nitrogen Content of the Blood in Diseases of the Liver and of the Biliary Tract. Arch. Surgery, 39(1):3-9, 5 figs., 1939.*

The lipid amino N of the blood of 22 patients without detectable hepatic disease, was determined by the method of Kirk, Page and Van Slyke. The average value was 1.24 mgs./100 gs., with a standard deviation of 0.62, 128 detns. were made in 43 patients with jaundice, hemorrhagic conditions, or probable liver damage. Normal values were obtained in those with obstructive or hemolytic jaundice without liver damage, while in those with obstructive or hemolytic jaundice without liver damage, while in those with obstructive jaundice and liver damage there was a consistent elevation above 2 mgs. There was no correlation noted between the hemorrhagic tendency and the lipid amino N level.—Courtesy of Biol. Abst.

JOHNSON, C. G., IRVIN, J. L. AND WALTON, CLARENCE: *The Free Choline and Phospholipid of Hepatic and Gall Bladder Bile. J. Biol. Chem., 131(2):425-437, 1939.*

Free choline was determined in ZnSO<sub>4</sub> filtrates of bile and total choline was determined after hydrolysis of protein-free filtrates of bile with Ba (OH)<sub>2</sub>. Choline was estimated gravimetrically by the Reinecke salt method. Only small amounts of free choline occurred in fresh hepatic and gall bladder bile of humans, dogs and hogs, but large quantities of combined choline were present. On standing (in ice box) with toluene and chloroform preservatives, the choline compound in bile decomposed rapidly with the formation of free choline. Desiccation of hog gall bladder bile by a vacuum drying process caused decomposition of most of the choline compound with the production of corresponding amounts of free choline. A portion of the combined choline of bile was extracted with ether-alcohol mixtures. This fraction was in the nature of phospholipid having a mole ratio of choline to P of 1:1. The isolation of lecithin from this fraction was reported. The possible presence in the ether-alcohol-extractable fraction of sphingomyelin or some other phospholipid with a choline to phosphorus ratio of 1:1 was not excluded.—Courtesy of Biol. Abst.

RIEDEL, C., CALDER, D. G. AND RAVDIN, I. S.: *Changes in Cholesterol Content of Hepatic Bile Subjects to Gall Bladder Activity. Am. J. Physiol., 129, No. 2, pp. 271-278, May, 1940.*

Due to the fact that there was a difference of opinion among authorities as to whether the gall bladder secreted cholesterol or not when in a diseased or normal condition the authors decided to repeat various experiments and extended them in order to confirm or deny their former assertions that the gall bladder wall neither secreted nor absorbed cholesterol when normal but did when damaged. After carefully repeating these experiments the authors





the ulcer and unselected groups is seven times that necessary for statistical significance. The ulcer patient therefore is more likely to be lighter in weight than the average person (Table II). It is of clinical interest

TABLE II

*The incidence of ulcer patients and unselected persons at various weights*

Weight	Under 120 Pounds	120-149 Pounds	150-179 Pounds	180 Pounds and Over	Total
250 ulcer patients	11%	49%	34%	6%	250 100%
7478 unselected men	4%	30%	41%	16%	7478 100%

that the heaviest ulcer patient (212 pounds) was more than 100 pounds lighter than the heaviest person in the unselected group (320 pounds).

#### THE CHEST CIRCUMFERENCE OF THE ULCER PATIENT

The ulcer patient has a definitely smaller chest circumference than is found in the unselected group. The average chest circumference of the ulcer patients was  $35.5 \pm 0.15$  inches with a standard range of from 33 to 38 inches while the unselected group (d) averaged  $37.0 \pm 0.07$  inches with a standard range of from 34 to 40 inches (Table III). A standard difference of 0.33 inches in the two means would show a statistical significance. Since the actual difference is over nine times the standard difference it appears that the small chest of these 250 ulcer patients cannot conceivably be a chance deviation from the usual. In Table III the difference in distribution of small and large chests is clearly evident. Only 8% of the ulcer as compared with 22% of the unselected group had very large chest circumferences. The opposite is true of the very small chests; 18% of the ulcer and 6% of the unselected

TABLE III

*The incidence of ulcer patients and unselected persons at various chest sizes*

Chest Circumference	Very Small Under 33 Inches	Small 33-35 Inches	Large 35-38 Inches	Very Large 39 Inches and Over	Total
250 ulcer patients	18%	41%	33%	8%	250 100%
1861 unselected men	6%	32%	40%	22%	1861 100%

group had small chests. The largest chest in an ulcer patient was 43 inches; in the unselected group there was one person with a 47 inch chest circumference.

(d) Of the 7478 persons in the unselected group, the chest and abdomen circumferences were abstracted for only 1861 of these men. This accounts for the difference in the size of the unselected group used in the height, weight, ponderal index and blood pressure tables from that of the chest, abdomen and body build indices. No basis of selection was used, and except for a slight difference in age, which makes the age of the 1861 group identical to that of the ulcer group, the other measures, height, weight, etc., were almost identical in the 7478 and 1861 unselected groups. For example, between the 1861 and 7478 group in height there is only 0.1 inch difference and in ponderal index a difference of only 0.04 in the measures of central tendency.

From these data it is evident that the ulcer patient has a smaller chest than does the unselected population. (See Chart 1).

#### THE ABDOMINAL CIRCUMFERENCE OF THE ULCER PATIENTS

The abdomen of the ulcer patients was smaller in circumference than the abdomen of the unselected group (Table IV). The average abdominal circumference of the ulcer patient was  $32.2 \pm 0.23$  inches with a standard range of from 29 to 36 inches while the unselected group showed an average of  $34.4 \pm 0.10$  inches with a standard range of from 30 to 39 inches. In order to be statistically significant the difference between the two groups would have to be only a quarter inch; the actual difference is over eight times the standard difference. More illustrative of the difference is the fact that 31% of the ulcer patients had abdomen circumferences less than 29 inches while only 15% of the unselected group had such a small abdomen, and while only 8% of the ulcer group had an

TABLE IV

*The incidence of ulcer patients and unselected persons at various abdomen sizes*

Abdomen Circumference	Small Abdomen		Large Abdomen		Total
	Under 28 Inches	28-31 Inches	32-35 Inches	36 Inches and Over	
250 ulcer patients	12%	39%	36%	13%	250 100%
1861 unselected men	5%	26%	35%	34%	1861 100%

abdomen larger than 36 inches, 26% of the unselected group had a large abdomen. Thus the ulcer patient is very likely to be smaller around the waist than the general population (Chart 4).

#### THE PONDERAL INDEX OF THE ULCER PATIENT

The raw measure of weight does not accurately measure the relative underweight or obesity of a person. For example, 150 pounds can mean either under or overweight, depending upon the height of the subject. An individual 60 inches tall would be overweight at 150 pounds, while a 74 inch person would be underweight. The ponderal index, weight divided by height, more accurately measures the weight factors; it establishes a more true normal weight and more quickly shows presence or absence of obesity. Because the measure of weight alone showed such a tremendous difference between the ulcer and the unselected group it would be expected that the ponderal index would also show a difference.

The mean ponderal index of the ulcer group is  $2.15 \pm 0.019$  with a standard range of from 1.86 to 2.45 while the unselected group with a mean of  $2.31 \pm 0.004$ , ranged from 1.99 to 2.63. Actually this difference in means or averages is eight times the standard difference necessary for statistical significance. Even more striking is the difference in the proportion of light and heavyweight persons in the ulcer and un-

selected groups (Table V). There were 40% lightweights in the unselected group as compared with 11% in the ulcer group. Using the formula,  $\sqrt{\frac{100}{N_1} + \frac{100}{N_2}}$ , the standard difference of the proportions was 1.9%. Actually the difference is three and one-half times this amount which indicates a significant difference. Similarly there were 18% heavyweights in the unselected group and only 7% in the ulcer group; the actual difference is over five times the standard and indicates a significant difference. Using the division as shown in Table III it is clear that the peak of the ulcer group is

difference could be purely a chance deviation. Therefore, there are far more underweights among the ulcer patients and far fewer overweights than is found in the unselected population (Chart 2). It is of clinical interest to note that in the most extreme obesity of the ulcer group the weight was only 3 times the height while in the unselected group one person's weight was 4 times his height.

### THE BODY BUILD OF THE ULCER PATIENT

Complicated indices have been worked out by anthropometrists to measure body build. For the purpose of

### CHEST CIRCUMFERENCE IN ULCER AND UNSELECTED PERSONS

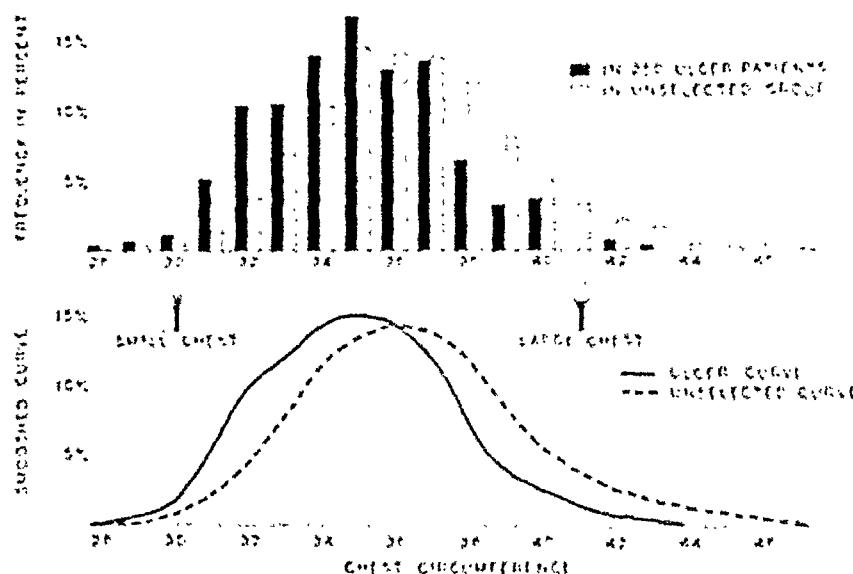


Chart 1. The distribution of chest circumference in the ulcer patients and in 1000 unselected persons. The upper frequency histogram shows the actual percentage of ulcer patients and unselected persons at each inch of chest circumference. The lower graph shows the cumulative percentage of the distribution. The ulcer group exhibits a far greater incidence in every chest circumference up to 36 inches. On the other hand in every chest group 37 inches and over there is a markedly decreased incidence of ulcer patients as compared with the unselected group. (Prepared by W.P.A.)

toward the lightweights while in the unselected group it tends toward the heavyweights. The Chi Square test (Table VIII) indicates an extremely significant difference in the distribution of weight in the two groups. There is less than 1 chance in a thousand that this

TABLE V

The incidence of ulcer patients and unselected persons of various weight

Weight Group	Ulcer Patients (%)	Unselected Persons (%)	Ratio
Lightweight	11%	40%	0.275
Mediumweight	44%	33%	1.333
Heavyweight	45%	27%	1.667

clinical investigation the complexity of this problem multiplies much of their usefulness. Further, there is no agreement among the many schools of anthropometry as to the accuracy and applicability of the four measurements. There is, however, considerable agreement among anthropologists that for the measurement of gross body build the width of the body must be estimated to the height. In this study the chest circumference is used as a measure of body width.

Using this chest-height measure as an index of gross body build the person with a low chest-height index is called a linear or slender type and the person with a high chest-height index is called a lateral or broad-chested type. The ulcer patient is usually a far more linear or slender type of person. The mean chest-height index for the ulcer group was  $57\% \pm 0.06\%$  with a standard range of from 1.49 to 3.66 while the unselected group averaged  $54\% \pm 0.06\%$  with a standard

range of from .499 to .587. This difference is nine times the standard difference and indicates an extreme deviation of ulcer patients toward the linear type of build. The incidence distribution of the two groups as compared in Table VI is strikingly illustrative of the wide variance in samples (Chart 3). A far greater proportion of ulcer patients had linear or slender build than did the unselected subjects. On the other hand the incidence of lateral or broad type builds is much smaller in the ulcer group. There was no extremely broad male with an ulcer whereas from the unselected distribution at least six ulcer males would be expected. The Chi Square test (Table VIII) shows that these

significantly more linear type of person than is found in a random sample of the non-ulcer population.

### THE CHEST:ABDOMEN RATIO OF THE ULCER PATIENT

To determine roughly the degree of abdominal protuberance in the usual ulcer patient, the circumference of the chest is compared with the circumference of the abdomen. When the chest measure is divided by the abdomen measure,  $\frac{\text{chest circumference}}{\text{abdomen circumference}}$ , the resulting index can be easily understood and manipulated. If the two measures are equal the index is 1 and the person is probably only slightly obese around the ab-

### PONDERAL INDEX IN ULCER AND NORMAL PERSONS

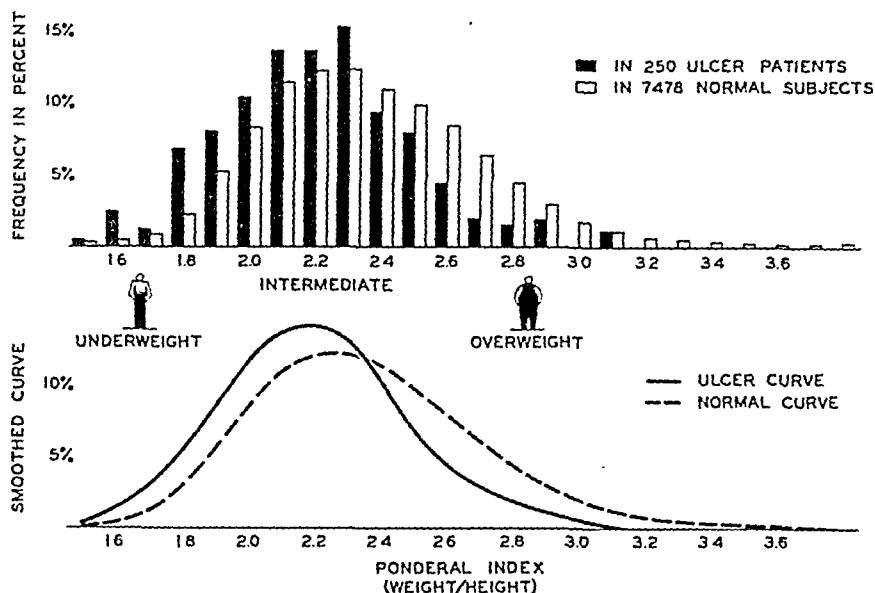


Chart 2. The distribution of ponderal index in 250 ulcer patients and in 7478 unselected persons. The upper frequency histogram shows the actual percentage of ulcer patients and unselected persons in each weight classification. The lower graph shows the smoothed curve of the distribution. The ulcer group contains a far greater incidence in the light and moderately lightweight classifications. In every heavyweight group (ponderal index 2.4 and over) there is a markedly decreased incidence of ulcer patients as compared with the unselected group. (Prepared by W.P.A.)

differences in distribution could not be chance differences. The most lateral ulcer patient had an index of only .66 as compared with .71 in the unselected group. These differences are real and the ulcer patient is a

TABLE VI

The incidence of ulcer patients and unselected persons in various build groups

Chest: Height Index	Linear (Slender Build) Under .48	Intermediate Build		Lateral (Broad Build) .60 and Over	Total
		.48-.53	.54-.59		
250 ulcer patients	9%	57%	31%	3%	250 100%
1861 un- selected men	6%	41%	42%	11%	1861 100%

domen. If the abdomen is smaller than the chest, as it should be, the resulting index is more than 1. If the abdomen has assumed pontifical proportions the index is less than 1. The larger the index the less bulging is the abdomen.

The ulcer patient on the average showed an index of  $1.12 \pm 0.004$  with a standard range from 1.05 to 1.19. Thus, most ulcer patients had an abdomen smaller than their chest. The unselected group on the other hand had an average ratio of  $1.09 \pm .002$  with a standard range from 1.01 to 1.17, an actual difference 8 times the standard difference. Thus the unselected groups tended, moreso than the ulcer group, to bulge at the waist.

The incidence relations are more illustrative of the trend (Table VII). A significantly appreciable number of the unselected group—10%—had abdomens larger

than their chests while very few of the ulcer group, only 2%, showed gross abdominal obesity. A much larger percentage of the ulcer group was concentrated in the indices denoting an abdomen smaller than the chest, 54% as compared with 40% in the unselected group. In other words it seems that gastro-duodenal ulcers are seldom accompanied by definite abdominal obesity.

### THE SURFACE AREA OF THE ULCER PATIENT

Although surface area is of little use either as a measure of weight or as a picture of build, it is of interest to observe how the height, weight measures

measure of both weight and build, although, from the nature of the calculation, it is more highly associated with the weight factor than with the build factor (c). The mean surface area of the ulcer group was  $1.76 \pm 0.009$  sq. m. with a standard range of from 1.61 to 1.91 sq. m. The unselected group showed a larger average of  $1.82 \pm 0.002$  sq. m. with a standard range of from 1.67 to 1.97 sq. m. To be statistically significant the difference between these means would need be only one-seventh of what it actually is, hence, the mean surface area of the ulcer group is significantly lower than in the unselected group.

The relative incidence of the two groups in the small

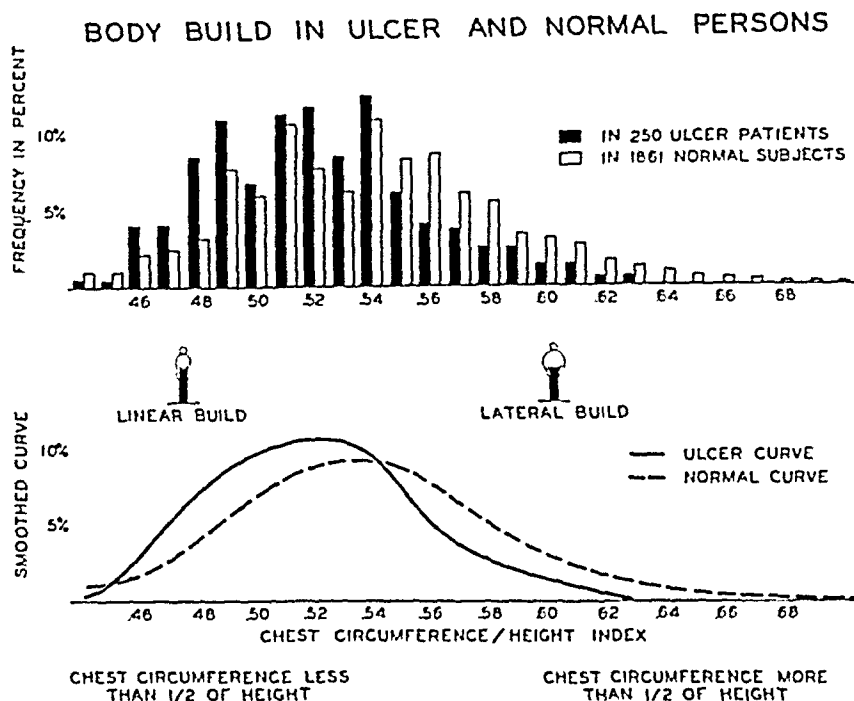


Chart 3. The distribution of body build in 250 ulcer patients and in 1861 unselected persons. The upper frequency histogram shows the actual percentage of ulcer patients and unselected persons in each weight classification. The lower graph shows the smoothed curve of the distribution. The ulcer group contains a far greater incidence of linear and intermediate build persons. In every lateral build group (chest:height index over .51) there is a markedly decreased incidence of ulcer patients as compared with the unselected group. (Prepared by W.P.A.)

manipulated in a slightly different manner compare with the ponderal index in differentiating the ulcer from the unselected groups. Surface area, as calculated by the standard Du Bois nomogram, is actually a

TABLE VII

The incidence of persons at various chest-abdomen ratios

Chest: Abdomen Ratio	Smaller Abdomen		Large Abdomen		Total
	1.2 and Over	1.1	1.0	Less Than 1.0	
250 ulcer men	12%	42%	44%	2%	250 100%
1861 un- selected men	0%	31%	50%	10%	1861 100%

and large surface area classifications is even more striking than the means. Thirty-five per cent of the ulcer group had a small surface area (under 1.70 sq. m.) and only 17% of the unselected group fell in this group. On the other hand only 16% of the ulcer group had a large surface area whereas 30% of the unselected group were large. The Chi Square test verified the significance of this difference and emphasized the fact that most of the significance of the deviation was due to the preponderance of small surface areas in the ulcer group. The ulcer patient is most frequently a person with a surface area smaller than is expected from the distribution in the unselected population.

(c) The coefficient of correlation of surface area to the chest:height index in the 250 ulcer patients is  $r = .285 \pm 0.58$ . The coefficient of correlation of surface area to the ponderal index (weight:height) is  $r = .742 \pm .025$ .

TABLE VIII

*Statistical summary of the comparisons between the ulcer and the unselected groups*

Measurement	Group	Mean*	Median	Mode	Standard Deviation of the Mean	Standard Error of the Mean	Skewness	Coefficient of Variation	Standard Range**	Total Range	Actual Difference in Means $\pm$ Standard Error of Difference	X <sup>2</sup> Chi Square Test	++ Very Significant + Slightly Significant 0 Unsignificant
Age (Years)	250 Ulcer	42.3	41.3	39.3	10.20	0.65	0.29	9.42	32.1 to 52.5	21 to 72			
	7478 Unselected	39.5	38.3	35.9	11.75	0.14	0.31	29.75	27.8 to 51.3	6 to 86***	..	..	..
	1861 Unselected	43.0	42.3	40.9	11.87	0.28	0.18	27.60	31.1 to 54.9	6 to 86			
Height (Inches)	250 Ulcer	67.9 (67.8)	68.0	68.4	3.00	0.19	-0.20	4.42	64.9 to 70.9	59 to 74	$\frac{0.21}{0.19} = 1.1$	$\frac{2.972}{n = 4}$	0
	7478 Unselected	68.2	68.3	68.5	2.83	0.03	-0.11	4.15	65.4 to 71.0	46 to 78			
Weight (Pounds)	250 Ulcer	145.9 (146.2)	141.9	142.3	22.09	1.40	0.18	15.11	123.8 to 168.0	81 to 212	$\frac{10.60}{1.43} = 7.4$	$\frac{38.005}{n = 2}$	+++
	7478 Unselected	156.5	154.4	150.2	24.06	0.28	0.26	15.37	132.4 to 180.6	48 to 320			
Chest Circumference (Inches)	250 Ulcer	35.5 (35.5)	35.5	35.5	2.45	0.15	..	6.90	33.05 to 37.95	28 to 43	$\frac{1.50}{0.165} = 9.1$	$\frac{44.058}{n = 4}$	+++
	1861 Unselected	37.0	36.8	36.4	2.83	0.07	0.21	7.63	34.17 to 39.83	22 to 47			
Abdomen Circumference (Inches)	250 Ulcer	32.2 (32.0)	31.9	31.7	3.61	0.23	0.08	11.28	28.6 to 35.8	22 to 44	$\frac{2.20}{0.257} = 8.5$	$\frac{66.521}{n = 4}$	+++
	1861 Unselected	34.4	34.2	33.8	4.24	0.10	0.14	12.33	30.2 to 38.6	20 to 49			
Ponderal Index Weight Height	250 Ulcer	2.15 (2.16)	2.15	2.13	0.295	0.019	0.102	13.66	1.85 to 2.45	1.37 to 3.07	$\frac{0.16}{0.019} = 8.4$	$\frac{38.210}{n = 2}$	++++
	7478 Unselected	2.31	2.28	2.22	0.328	0.004	0.274	14.20	1.99 to 2.53	1.04 to 4.00			
Chest: Height Index	250 Ulcer	0.525 (0.525)	0.523	0.519	0.036	0.002	0.167	6.86	0.489 to 0.561	0.44 to 0.66	$\frac{0.018}{0.002} = 9.0$	$\frac{37.323}{n = 4}$	+++
	1861 Unselected	0.543	0.543	0.543	0.044	0.001	..	8.10	0.499 to 0.587	0.38 to 0.71			
Chest: Abdomen Index	250 Ulcer	1.12 (1.12)	1.11	1.09	0.059	0.004	0.430	6.16	1.05 to 1.19	0.94 to 1.33	$\frac{.0300}{.0045} = 6.7$	$\frac{38.345}{n = 3}$	+++
	1861 Unselected	1.09	1.08	1.06	0.077	0.002	0.390	7.06	1.01 to 1.17	0.82 to 1.52			
Surface Area (Du Bois formula)	250 Ulcer	1.76 (1.76)	1.76	1.76	0.15	0.009	..	8.41	1.61 to 1.91	1.26 to 2.17	$\frac{.0500}{.0092} = 6.5$	$\frac{55.819}{n = 3}$	++++
	7478 Unselected	1.82	1.81	1.79	0.15	0.002	0.20	8.08	1.67 to 1.97	0.81 to 2.43			
Systolic Blood Pressure (mm. of Hg.)	250 Ulcer	116.3 (115.5)	113.3	108.3	16.40	1.04	0.16	14.16	100 to 133	84 to 190	$\frac{4.70}{1.06} = 4.4$	$\frac{36.359}{n = 4}$	+++
	7478 Unselected	121.0	119.3	115.9	17.35	0.20	0.29	14.34	104 to 138	62 to 250			
Diastolic Blood Pressure (mm. of Hg.)	250 Ulcer	72.3 (72.5)	72.0	71.9	10.44	0.66	0.14	14.40	62 to 83	40 to 130	$\frac{2.10}{0.67} = 3.1$	$\frac{8.300}{n = 4}$	+
	7478 Unselected	74.4	73.3	71.1	10.41	0.12	0.32	14.03	64 to 85	40 to 140			

\*All figures except age are adjusted to the age of the unselected group, unadjusted figure in parenthesis.

\*\*Standard Range  $\pm$  one standard deviation from the adjusted mean.

\*\*\*A few very young persons, under 15 years of age, were excluded from all group totals.

# THE BLOOD PRESSURE OF THE ULCER PATIENT

In view of a correlation between body build and blood pressure (12) in which the hypertensive patient was described as a lateral type build with a tendency toward overweight, it is interesting to compare the blood pressure in the ulcer patient who tends towards the opposite type of build and weight. Because of the relation between linear build and low blood pressure we should expect the ulcer patients to show pressures

lower than the unselected group. This is born out in the case of systolic pressure. The ulcer group had a mean systolic pressure of  $116.3 \pm 1.04$  mm. with a standard range of from 100 to 133 mm. The unselected group had a mean pressure of  $121 \pm 0.20$  mm. with a standard range of from 104 to 138 mm. The difference in the averages of the two groups is almost five times the standard difference and hence is a significant finding. As should be expected the preponderance of this difference is caused by the excessive distribution of

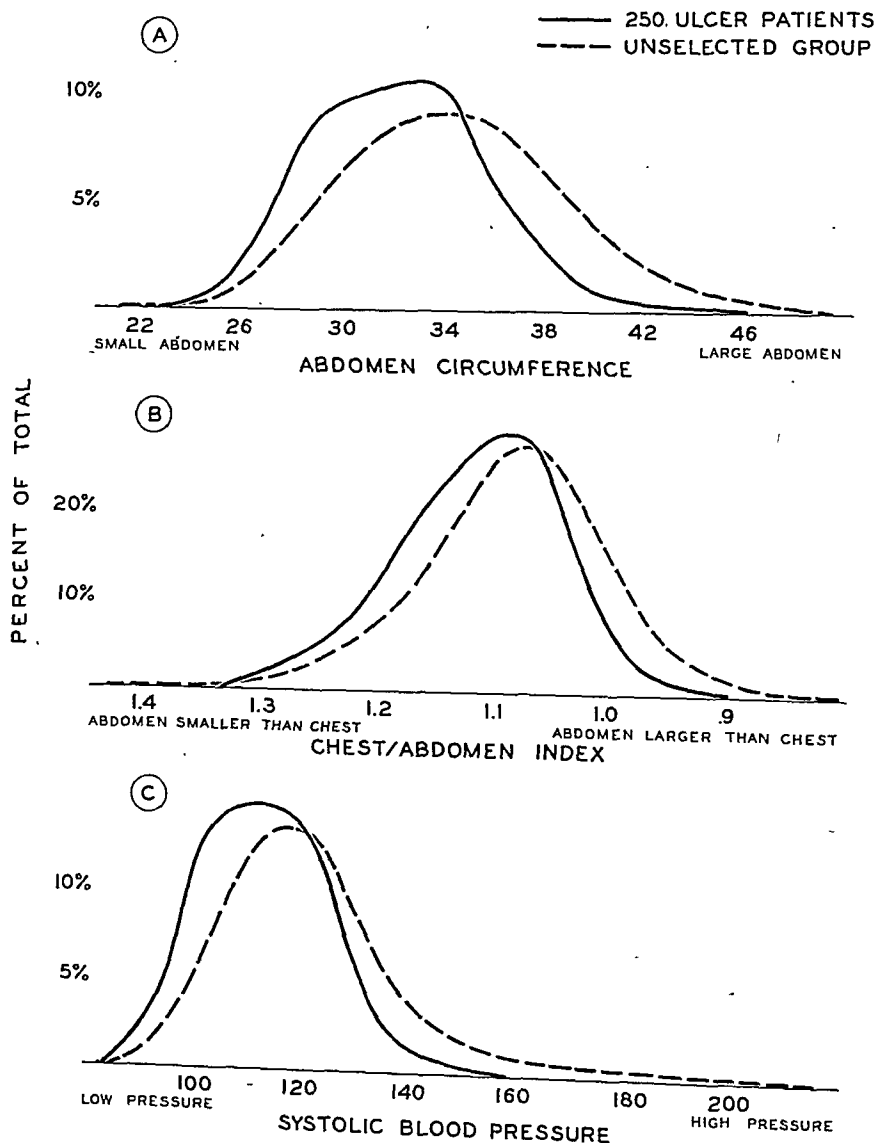


Chart 4. Comparison of the ulcer and unselected groups in various measurements (smoothed curves). (A) The ulcer group contains a far greater incidence of small abdomens. At every inch over 34 there is a marked decrease in the incidence of ulcer patients as compared with the unselected group. (B) The ulcer group tends to have abdomen circumferences much smaller than their chest circumference. Very few ulcer patients have abdomen circumferences equal to or greater than their chest circumference. (C) The ulcer group contains a far greater incidence of systolic pressures under 120 mm. At every pressure over 120 mm. there is a markedly decreased incidence of ulcer patients as compared with the unselected group. (Prepared by W.P.A.)

low pressures in the ulcer group; 37% of ulcer patients had systolic pressures under 110mm. while only 22% of the unselected group registered these low pressures. Conversely the ulcer group showed only 5% of systolic pressures 140mm. or over while the unselected group contained almost 11% (Chart 4). The Chi Square test emphasizes the improbability that this could be a chance difference (Table VIII). It is rare for an ulcer patient to register a high systolic pressure. Only four patients—less than 2% recorded pressures over 190mm.

The diastolic pressure picture is somewhat different. The ulcer group showed a mean diastolic pressure of  $72.3 \pm 0.66$ mm. with a standard range of from 62 to 83mm. The unselected group's average was  $74.4 \pm 0.12$ mm. with a standard range of from 64 to 85mm. The actual difference in pressures is in the direction that would be expected but is only three times the standard difference and hence has only a slight statistical significance in this sample of ulcer patients. The compared distributions bear this out; 35% of ulcer patients and 30% of the unselected group had a diastolic pressure under 60mm. 5% of ulcer patients and 7% of the unselected group had diastolic pressure over 90mm. The Chi Square test indicates a probability of about 8 in 100 that this difference could be due to chance. This does not mean that the ulcer patients do not tend to have a lower diastolic pressure than the unselected group as shown by the data. It means merely that this group shows a difference which might possibly have been due to chance. It is fairly definite that the systolic pressure of the ulcer patient is lower than would be expected in a sample of the general population. The diastolic may be slightly lower, but the difference is of little significance in this sample.

### DISCUSSION

One important consideration in the etiology of any disease can be phrased in the question, "What type of person is susceptible?" "What does he look like?" In answering this question about the ulcer patient the previous work of Hurst, Draper and others is confirmed. The ulcer patient will more frequently be of a slender or linear build than is usually found in the unselected population, and will be lighter in weight, smaller in chest and abdominal circumference and his abdomen will tend to be smaller than his chest.

These facts concerning the build of the ulcer patient are of value to the clinician in the differential diagnosis of dyspepsia. It is of considerable value to know that a given individual with upper abdominal distress is less likely to have an ulcer if his chest circumference is 40 inches or over. If the patient is considerably overweight the physician's diagnosis should be tempered by the fact that ulcer is very rare in a person who weighs over 180 pounds. If the patient has a large abdominal protuberance—2 to 3 inches in excess of his chest—it is highly improbable that he has an ulcer. Doubt should be cast upon the diagnosis of ulcer in a patient whose systolic blood pressure exceeds 150mm. None of these criteria of themselves or in combination exclude the diagnosis of ulcer but they occur so rarely in the ulcer patient that the weight of evidence would argue against it. Contrariwise, the diagnosis of ulcer becomes more probable if the patient is of the slender or linear build, if he is underweight, or if his systolic pressure is low. No one contends that the build type predisposes to the presence or absence

of ulcer or any other disease. The importance of body build in disease is not based upon the premise that "anatomic habitus is one of the causes of disease." It is incorrect to suppose that Hurst, Draper or others have assumed this position. Such a contention clouds the issue. The importance of the study of constitution in disease is in the study of the individual as a whole, and of his hereditary background, so that all factors related to disease, genetics, morphology, personality, clinical and laboratory findings may be fitted together to form a complete mosaic. Use should be made of the simple and proved measurements of gross body build in ulcer even though they constitute only a small portion of the completed anthropometric picture.

The gross morphology of the ulcer patient as presented in this paper raises many intriguing questions demanding further research. Why does the lateral or broad chested individual usually escape ulcer only to develop cardiovascular degeneration in later years? What are the underlying biochemical and neuromuscular patterns that lead to selectivity in disease? Why does ulcer occur so predominantly in the linear, narrow chested person who is usually underweight and has a characteristic personality? For the recognition of a definite build type in the ulcer patient should serve further to focus attention upon the particular personality type that accompanies it. Accordingly, we are led to consider the significance of the emotional factor which is dominant in the ulcer problem.

While this picture of the ulcer patient as a lightweight, linear or slender person is not new—observing physicians have long recognized the type—there has been some discussion as to the relevancy of the findings. The outstanding statistical study in the literature that questions the build distinction of the ulcer patient is that of Feigenbaum and Howat. The authors of this excellent anthropometric study arrived at conclusions opposite to those cited in this paper. Because many gastro-enterologists have accepted the conclusions of Feigenbaum and Howat, it is important that considerable space be given to a reevaluation of their data. These authors used 37 anthropometric measurements to differentiate the ulcer from other patients. They worked upon the assumption that most of the measures would have to show significant differences in order to show a build factor in a disease. Among the measures they used were nail length and breadth, finger circumference, ear length and ear width, interpupillary space, etc. The role of these measurements in the study of body build has not been agreed upon, there being considerable divergence of opinion among the various schools of anthropometry. These measures and many others they used may eventually prove of some value—finer anthropometric research should not be discouraged—but they contribute very little to the understanding of gross build types. Our problem in the study of body build is to differentiate first the gross and easily obtained measurements of value to the clinician. There is substantial agreement among anthropometrists as to what these measurements are. As Davenport (11) has pointed out, "When I look at man . . . and think, 'he is slender,' it is because I make a mental comparison of his breadth (of shoulders or chest) with his height and find that his breadth in comparison with that of most men I know of that height is small; or if he is stout the diameter of the

chest is large in relation to stature. It seems probable that breadth in relation to height gives the best expression of the popular idea of build." It is this conception of build that we discuss in this paper. When we select those measurements of Feigenbaum and Howat which are comparable to ours and are most useful in differentiating gross build types, there is a complete agreement with our data. For example, Feigenbaum and Howat state, "The thoracic antero-posterior diameter was deeper in the diabetic than in the peptic ulcer group, both with the males and the females. The same relationship was discovered to exist in the thoracic lateral diameter and in the chest circumference. And so it can be stated that the diabetic population has a deeper, a broader and a more voluminous chest than the peptic ulcer race." These authors also found a significantly lower weight and ponderal index of the ulcer patients which is precisely what our study showed. The measures which do not show significant differences are those which have no bearing on gross build. It is well to emphasize that it is not necessary for the majority of all possible anthropometric measures to show differences in order to prove a build type for the ulcer patient. Nor does every patient have to be of 'the type.' It is only necessary to demonstrate the predominance of one or many of the gross measures of build in certain diseases to show a constitutional factor.

#### CONCLUSIONS

1. The gross measures of body build, weight, and blood pressure in 250 men with gastro-duodenal ulcer as proved by X-ray and history are compared with a control group of 7478 men.

2. The ulcer patient was found to differ from the control group in every measure studied except height.
3. The ulcer patient tends to be normal or underweight. He is seldom overweight.
4. The chest circumference of the ulcer patient tends to be much smaller than is found in an unselected population. Only rarely does a person with a large chest have an ulcer.
5. The abdomen circumference at the level of the umbilicus is smaller in the ulcer than in the unselected groups.
6. The body build as measured by the chest:height index shows that the ulcer patient usually has a slender, narrow or linear type build. He is seldom of the broad-chested or lateral build and almost never extremely lateral.
7. The chest:abdomen index shows that the ulcer patient, more so than in the unselected group, has little tendency to develop abdominal protrusion. His abdomen is smaller than his chest.
8. The surface area of the ulcer patient is smaller than is expected from the distribution of an unselected group.
9. The systolic blood pressure of the ulcer patient tends to be lower than in the unselected group.
10. The diastolic blood pressure does not show a very significant difference but is slightly lower in the ulcer than in the unselected group.

#### ACKNOWLEDGEMENT

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## An Evaluation of the Meulengracht Regime in the Treatment of Bleeding Peptic Ulcer\*

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THE frequency with which peptic ulcer is encountered in medical practice is admittedly high. A fairly large percentage of ulcer cases are complicated by the occurrence of hemorrhage, as manifested by

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hematemesis, melena, or both. This has been variously reported in 18 to 38 per cent of cases (Pfeiffer (1), Blackford, Smith and Affleck (2) and Goldman (3)). There can be no doubt that a great number of ulcer patients never seek medical aid. Although on the face of it this would seem to lower the percentage of the



occurrence of bleeding as a complication, it must also be borne in mind that many mild bleeders never consult the physician.

Because of the dangers of hemorrhage, with its attendant high mortality rate, serious consideration has been given to its management. Various dietary regimes have been employed. The one regarded as most satisfactory, until 1933, consisted of a period of starvation followed by a rigidly restricted food intake which was slowly increased. Even with this generally accepted method of treatment, the mortality rate ranged from 3.4 to 25 per cent, as reported by various authors (see Table I). It will be noted from the table that where surgical treatment has been used, the death rate has been as low as 4.3 per cent and as high as 32.7 per cent.

It is little wonder, therefore, that when Meulengracht (20a) in June, 1933, reported a mortality rate of only 1 per cent with the method of treatment he was using, it was quickly tried by others. The essential features of Meulengracht's method are, first, that the patients are fed from the very onset of hemorrhage and, second, that they receive liberal food allowance consisting of a puréed high caloric, high vitamin diet.

In all fairness to other investigators, it should be pointed out that prompt and fairly liberal feedings in the treatment of bleeding ulcers were recommended before Meulengracht's first publication on the subject. For example, in 1927, Andresen (21) suggested the immediate administration of a gelatin-water mixture at two hour intervals, with the addition of other nutri-

ments on the second or third day. He decided to alter his therapeutic procedure because of his conviction that the stomach is less active when full than when empty. In addition, he had observed that patients with bleeding ulcers, who continued on a full diet, frequently fared well. Unfortunately, Andresen's method was not widely adopted and popularized.

Meulengracht was prompted to change the manner in which he treated bleeding ulcer cases by observations in part similar to those of Andresen. Many patients who had not sought medical aid and had continued on their usual diet apparently made uneventful recoveries. Some patients with protracted hemorrhage stopped bleeding when fed. Furthermore, some patients, despite the most rigid dieting, died, apparently from exhaustion rather than from the extent of the hemorrhage. Therefore, it seemed to him of questionable advantage to starve a patient when he is presumably in special need of support.

The puréed diet adopted by Meulengracht in 1931 contained approximately 2300 calories and was administered as follows:

- 6 A. M. Tea, white bread and butter.
- 9 A. M. Oatmeal with milk, white bread and butter.
- 1 P. M. Dinner consisting of any of the following in unrestricted amounts: meat balls, timbale, broiled chops, omelette, fish balls, gratin of fish, vegetable or meat, mashed potatoes, puréed vegetables, cream of

TABLE I  
*Mortality statistics for older methods of treatment*

Authors	Year	Hospital	Type of Treatment	Number of Cases	Number of Deaths	Mortality %
Bulmer (4)	1932	General	Medical	111	18	16.0
Chiesman (5)	1932	St. Thomas	Medical	191	..	25.0
Allen and Benedict (6)	1933	Mass. General	Surgical and Medical	138	20	14.5
T. Christianson (7)	1934	Communehospital	Medical	289	23	7.9
Umber (8)	1935	Berlin-Westend Clinic	Medical	433	41	9.5
Emery and Monroe (9)	1935	Peter Bent Brigham	Medical	384	20	5.2
Gordon-Taylor (10a)	1935	Middlesex	Surgical	..	..	21.0
Hesser (11a)	1936	Linköping	Medical	304	15	5.0
Finsterer (12)	1936	Univ. of Vienna	Surgical ( $< 48$ hrs.) ( $> 48$ hrs.)	46 55	.. ..	4.3 32.7
Hurst and Ryle (13)	1937	Guy's	Medical	82	4	4.8
Babey and Hurst (14)	1937	(Data accumulated from 22 practitioners)	Medical	525	8	1.5
Tidy (15)	1937	St. Thomas	Surgical and Medical	30	5	17.0
Blackford, Smith and Affleck (2)	1937	Mason Clinic	Surgical and Medical	36	6	17.0
Pfeiffer (1)	1938	Lanenau and Abington Memorial	(Medical) (Surgical)	40 22	3 5	7.5 22.7
Copland (16)	1938	Touro Infirmary	Medical	32	7	22.0
Goldman (3)	1938	San Francisco	Medical and Surgical	349	52	15.0
Browne and McHardy (17)	1939	Tulane	(Medical) (Surgical)	115 14	4 3	3.4 21.4
Turnbull and Sagi (18)	1939	Northwestern	Medical	77	4	5.3
Crohn and Lerner (19)	1939	Mt. Sinai	Medical	216	14	6.5

TABLE II

*Age and sex distribution, and duration of hemorrhage before admission in Meulengracht and control series*

	Number of Cases		Age in Years								Duration of Hemorrhage Before Admission (Average)				
			10-19		20-29		30-39		40-49			50-59		60-	
"Starvation-Sippy" Series	Male	Female	M	F	M	F	M	F	M	F	M	F	M	F	4.3 days
	62	10	3	0	10	3	16	1	13	0	13	4	7	2	
Totals	72		3		13		17		13		17		9		
Meulengracht Series	Male	Female	M	F	M	F	M	F	M	F	M	F	M	F	4.3 days
	15	6	0	0	5	1	5	1	2	3	3	0	0	1	
Totals	21		0		6		6		5		3		1		

vegetables, vegetable soup, stewed apricots, applesauce, gruel, rice and tapioca pudding.

3 P. M. Cocoa.

6 P. M. White bread and butter, sliced meats, cheese and tea.

In addition, patients received a teaspoonful, three times a day, of a powder containing the following:

Sodium bicarbonate  
Magnesium subcarbonate aa 15.0  
Extract hyoscyamus 2.0

They were also given ferrous lactate 0.5 gm. t.i.d. It must be added that a few of his patients, who were markedly exsanguinated on admission, received one or two transfusions immediately.

In all their published reports, Meulengracht and his colleagues (20a, b, c, d, e, f), (22) emphasize the fact that only cases of serious bleeding were included. His publication of October, 1937, is based on a total of 368 cases. Only five of these patients died, giving a mortality rate of 1.35 per cent. This represents a striking improvement over the lowest figures previously reported by those employing either the former medical regime or surgery. His encouraging results prompted us to adopt the method outlined by him in a series of patients with hemorrhage from peptic ulcers. Our experiences are contained in this report.

#### CLINICAL MATERIAL AND RESULTS

Our series consists of 21 patients, all of whom showed evidence of fairly extensive blood loss. The diet outlined above was employed in each instance

along with a powder consisting of the following given three times a day after meals:

Sodium bicarbonate 2.0  
Magnesium subcarbonate 2.0  
Extract of hyoscyamus 0.1  
Ferrous lactate 0.5

Five of our patients required transfusions.

Of our 21 patients, 11 were service cases and 10 private. Their ages ranged from 22 to 63 years. Fifteen were males, 6 females (Table II). Seventeen, or 81 per cent of the group, had ulcers proven roentgenologically, surgically or by postmortem examination (Table III). One case showed X-ray findings suggestive of ulcer. The remaining three cases gave no previous ulcer history and negative X-rays after the bleeding had subsided. In these, the diagnosis rested on well-founded clinical evidence.

For comparative purposes, we have studied the results obtained in an unselected group of 72 patients with bleeding peptic ulcer who had been treated with the older medical method. Twenty-eight of this group were service cases, 44 private. Although different members of the staff supervised the treatment of these patients, it was essentially the same: a period of starvation up to several days with infusions, followed by minimal feedings in slowly increasing amounts, usually in the form of a Sippy diet. Some of these patients received transfusions. In both our groups, the interval which elapsed between the onset of the hemorrhage and the time of admission to the hospital averaged 4.3 days. In this respect, therefore, the two series are comparable. Reference to Table II shows that in both groups males exceed females, there being 2.5 times as

TABLE III

*Extent of proof of ulcer in Meulengracht and control series*

	Total No. Cases	Proven Ulcers*		Partial Corroboration**		Ulcer Diagnosed Only Clinically	
		No. Cases	%	No. Cases	%	No. Cases	%
"Starvation-Sippy" Series	72	56	77.8	2	2.8	14	19.4
Meulengracht Series	21	17	81.0	1	5.0	3	14.0

\*Proven by X-ray, surgery or autopsy.

\*\*X-ray suspicious for ulcer.

TABLE IV  
*Comparative results obtained in our two series*

	Number of Deaths	Mortality Per Cent	Number of Perforations	Perforations Per Cent	Days in Hospital (Average)	Days in Hospital of Service Cases Only (Average)
"Starvation-Sippy" Series	<sup>8</sup> M. 25    M. 56 M. 38    M. 62 M. 40    M. 64 M. 46    F. 35	11.1	<sup>1</sup> M. 56	1.4	21	26.2
Meulengracht Series	<sup>1</sup> M. 58	4.76	<sup>2</sup> F. 41 F. 63	9.5	27	34.1

many in our Meulengracht group, and more than 6 times as many in our "starvation-Sippy group." The age distribution appears essentially the same in both groups, the occurrence of bleeding ulcer being relatively rare below the age of 20.

We were primarily interested in the number of deaths which occurred with the two methods of treatment. Comparative figures for the two groups are included in Table IV. Among our 21 patients treated with the Meulengracht diet there was one death, a male, aged 58. The mortality rate was, therefore, 4.76 per cent. This compares very favorably with 8 deaths in our control group, or a rate of 11.1 per cent. This latter figure is in line with the results reported by others for patients similarly treated. In evaluating the 4.76 per cent mortality rate, we must bear in mind the small series upon which it is based.

On the "starvation-Sippy" regime, the average hospital stay of our patients was 21 days. We were surprised to find that with the Meulengracht regime the period of hospitalization was 27 days. These comparative figures are at variance with those reported by Meulengracht (20f) and Boyd and Schlachman (23). The former states that since he introduced his regime, the period of hospitalization has averaged five weeks, representing a decrease of one to three weeks. It is worth noting that Boyd and Schlachman were able to allow patients on the new regime out of bed in two weeks instead of five to six weeks. Realizing that

the duration of hospitalization for service cases is generally longer than for private patients suffering from the same ailment, we have determined the average hospital stay for our service cases only in each group. We find that the relationship previously noted by us still holds. On the "starvation-Sippy" regime our patients were discharged after a period of 26 days, whereas the group on the Meulengracht regime was hospitalized for 34 days.

A matter of interest to us has been the occurrence of perforation in patients who are bleeding from an ulcer. We are well aware of the fact that the co-existence of these two complications has always been considered a rarity. As a matter of fact, in our control group of 72 cases, only one instance of perforation was observed (1.4 per cent). This occurred in a male patient, aged 56, and terminated fatally. On the other hand, of our 21 cases treated with the Meulengracht method, two perforated, making an incidence of 9.5 per cent. These patients were females, aged 63 and 41, respectively, and both recovered following surgical intervention.

#### DISCUSSION

We have gathered from the literature the mortality statistics reported by various investigators who have employed the Meulengracht regime in the treatment of bleeding ulcers. These are given in Table V and consist of nine series of cases, including our own.

TABLE V  
*Mortality statistics accumulated from the literature in cases treated with Meulengracht diet*

Authors	Year	Hospital	Number of Cases Treated	Number of Deaths	Mortality Per Cent
Gram (24)	1936	Sundby	106	2	2.0
Gubergritz (25)	1936	University of Kiev	15	0	0.
Meulen-gracht (20f)	1937	Bispebjerg	368	5	1.36
Witts (26)	1937	St. Bartholomew	24	0	0.
Boyd and Schlachman (23)	1938	Metropolitan	15	0	0.
Herlihy (27)	1938	Lewisham	..	0	0.
Crohn (19)	1939	Mt. Sinai	23	2	8.6
Mayer and Lightbody (28)	1939	Receiving	71	1	1.4
Chasnoff, Leibowitz and Schwartz	1939	Beth Israel	21	1	4.76
Total			643	11	1.7
Total (Without Meulengracht's figures)			276	6	2.18

Herlihy's (27) group is of importance in that he reports no deaths, but he fails to state the total number of cases upon which his report is based. Combining all the figures given in the table yields a mortality rate of 1.7 per cent. Even if Meulengracht's cases are excluded, the percentage is only 2.18. This is still a marked improvement over the results obtained with the earlier medical method of treatment (compare with Table 1).

One point repeatedly stressed by Meulengracht and his co-workers is the feeling of well-being of the patients while on liberal feedings. In our group we have also observed this mental and physical comfort. Furthermore, those of our cases (one-third) who had bled previously and had then been treated with the older method, later expressed a definite preference for the therapeutic regime which allowed them food and liquids from the very beginning of their hospitalization.

In regard to the question of duration of hospitalization, our findings are not in accord with those of other investigators. As shown above, our patients on a Meulengracht regime were hospitalized about a week longer than those on the "starvation-Sippy" regime. Moreover, it must be pointed out that we did not deliberately keep these patients in the hospital longer because of our special interest in the problem. The same criteria were employed in both groups to determine the time of discharge.

The matter of the occurrence of perforation as a further complication in bleeding ulcer is of great importance. Most authors report this as a relatively rare combination; e.g., Browne and McHardy (17) 1.5 per cent, Tage Christianson (7) 1.0 per cent, Allen and Benedict (6) 3.0 per cent, Hurst and Ryle (13) 1.2 per cent, Gordon-Taylor (10b) 2-3 per cent, Goldman (3) 2.0 per cent, Blackford, Smith and Affleck (2) 1.9 per cent. These figures are in accord with that of our own control series, 1.4 per cent. This contrasts sharply with the 9.5 per cent occurrence in our Meulengracht series. The question that immediately presents itself, therefore, is the part played by large feedings in bringing about this complication. This seems a good possibility which ought to be borne in mind when this method of treatment is employed. In this connection it should be pointed out that Meulengracht (20f), in his series of 368 cases, has apparently encountered this complication only once—and that in the form of a jejunal ulcer—and that Gram (24) reports its occurrence only once in a series of 106 cases. The contributory role of an underlying arteriosclerosis poses another problem. Despite the fact that one of our two cases of perforation was in a patient aged 41, it is interesting to note that in our entire Meulengracht series there were only four patients in the arteriosclerotic age group (i. e., above 50) and, of these, one showed this added complication. Furthermore, the one perforation observed in our control group occurred in a patient of 56. Although these facts do not warrant drawing definite conclusions, particularly in view of the small number of cases studied, they nevertheless indicate the need for further careful observations in this direction.

The rationale of Meulengracht's early feedings is further supported by certain interesting experimental work on the physiology of the stomach. It has long been taught that the empty stomach is least active,

and thus aids in clotting and healing at the site of the hemorrhage. However, the studies carried out by Oline Christianson (29a, b) in 1931 indicate that the reverse is the case. Working with human subjects, she introduced into the stomach an inflatable balloon connected to a manometer and obtained gastrophysiology. She found that the empty, or nearly empty, stomach is alternately at rest and in a state of forceful contraction. On the other hand, the fairly well-filled stomach is at all times relatively inactive. Continuous contraction waves in the latter are much weaker than those in the empty stomach, and the greater the food content, the longer are the periods of rest.

The advisability of the use of alkaline powders, along with the feedings, is borne out by the experimental work of Hunter (30). In 1928, he demonstrated that the clotting time of human blood is markedly prolonged when treated with gastric juice. The previous addition of soda bicarbonate lessens appreciably this action of the gastric juice.

Of general interest in the consideration of hemorrhage from peptic ulcer is the matter of the duration of the active bleeding. In the past most clinicians have used as criteria not only the general condition of the patient, blood picture, blood pressure and pulse, but also the presence of blood in the stool. To rely upon the disappearance of occult blood as an indication of cessation of hemorrhage is apparently based upon a mistaken concept. The ingenious experiments performed by Hesser (11b) in 1934 throw a new and interesting light on the subject. In a series of 72 bleeding ulcer patients, he found, using the Weber test, that the stools became negative for occult blood in anywhere from a few days to six weeks, and tabulated his results as follows:

Number of Days After Admission	0-7	8-14	15-21	22-28	29-35	36-42
Weber Negative: Number of Cases	5	24	31	5	5	2

Usually occult blood persisted several days to a week after evidence of gross blood in the stool had disappeared. In order to determine the motility of the colon in bleeding ulcer cases, he then fed two to four tablespoonsful of 20 per cent barium sulphate suspension in water to a group of 54 bleeding patients directly after admission. Stool examinations for barium were done daily, and showed that for the most part it required 8 to 21 days for the passage of all of the barium, but sometimes as long as 42 days. These findings are shown below:

Number of Days After Admission	0-7	8-14	15-20	21-28	29-35	36-42
Barium Negative: Number of Cases	8	26	15	2	1	2

Of especial interest is the fact that simultaneous examination of the stools for blood and barium showed almost parallel results. Hesser concluded logically that the continued presence of blood in the stool was due to delayed motility of the colon rather than to persistent bleeding or oozing. Only where blood was present for any length of time after barium had completely disappeared from the stool did he feel justified in assuming that bleeding had been prolonged.

No discussion of the treatment of bleeding ulcers can be complete without some reference to the claims made by the proponents of surgical intervention. Opinions vary as to the value of this procedure. All agree that the vast majority of cases can be adequately handled medically, some even going so far as to reject the use of surgery completely (Witts (26)). Most

authors admit that a certain small percentage (according to Lahey (31) and Emery and Monroe (9), 5 per cent) of these cases will fare poorly under any form of treatment. The ability to recognize early these apparently hopeless cases is a point in dispute. Tidy (15) states that such patients present a clinical picture by which they can be readily distinguished. We cannot subscribe to this view but rather feel, with Emery and Monroe, that the suggested criteria for their recognition are inadequate.

### CONCLUSIONS

1. The results obtained in a series of 21 cases of bleeding peptic ulcer treated with the Meulengracht regime are presented. These are compared with a control group of 72 cases treated with the older "starvation-Sippy" method.

2. Mortality statistics of all cases treated with the Meulengracht regime, thus far reported in the literature, are presented. These are compared with similar

statistics for the older methods of treatment.

3. The mortality rate in the Meulengracht series was 4.76 per cent. This is a decided improvement over the 11.1 per cent mortality in the control group.

4. The patients receiving early liberal feedings manifested a well-being not noted in those under the older method of treatment.

5. The average period of hospitalization was not decreased under the Meulengracht regime.

6. Two of our 21 cases (9.5 per cent) were further complicated by the occurrence of perforation, whereas this occurred in only one patient in our control series (1.4 per cent). The possible role played by the increased feedings is considered.

We acknowledge with thanks the graciousness of those members of the Attending Staff who permitted us to include their cases, both private and service, in this report. We are indebted to Dr. I. W. Held for his encouragement and suggestions.

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## Functional Bowel Disturbance and Milk Allergy—Bedside Diagnosis\*

By

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THE role of allergy to food in the causation of abdominal distress and disturbance in the function of the gastro-intestinal tract has been amply elucidated in the medical literature (1). It has been pointed out that such food allergy is a frequent and important

factor in the syndrome of the spastic colon; and that recognition and removal of the exact food offender often results in spectacular relief of the acute and chronic bowel symptoms which are part of this syndrome. In spite of this the diagnosis of food allergy of the colon is still too often overlooked.

The reason for this may be assumed to be twofold. First, the possibility of food allergy does not even enter the physician's mind. That the physician be

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constantly aware of the possibility of the presence of food allergy is considerable assurance that it will be recognized when present. This happy state of affairs is often only reached when he himself has gone through a distressing personal experience with his own spastic colon, and after long travail and ineffective symptomatic treatment, finally, often accidentally, becomes aware that he is allergic to a certain food, and by its removal obtain dramatic and complete relief. One can be sure that such a physician will always remain "food-allergy conscious" in his analysis of obscure bowel distress.

However, even when the possibility that food allergy may be the cause of an otherwise unexplainable colonic disorder enters the physician's mind, the diagnosis may nevertheless be approached with subconscious trepidation, because it brings to his mind the extensive, time consuming, and costly armamentarium of allergic diagnosis (skin testing, elimination diets, food diaries); or even the necessity of the complete transfer of the patient, often after an already extensive and costly general and gastro-intestinal workup, to the specialist in allergy, with no assurance that when all is said and done, the diagnosis will be substantiated, the offending food or foods found, or therapeutic benefit obtained. The orthodox and all inclusive diagnosis of spastic colon, and its orthodox, even if ineffectual, treatment by rest, heat, anti-spasmodics and "bland" diet (often made up mostly or entirely of the unsuspected cause of the disorder e.g. milk) then serves as a welcome haven to the harassed diagnostician, and the disturbing thoughts of allergy are only too readily dismissed. The demonstration that at least in one group of cases caused by a common allergen, namely, milk and its derivatives, and comprising a considerable portion of the total cases of colonic food allergy, the diagnosis may be one of such simplicity as to be practically a bedside one, might tend to allay such apprehension and make this diagnosis one more generally considered. This forms the primary object of the present communication.

The position of milk allergy is unique in that first, it occurs relatively frequently, so that it is the cause of a considerable percentage of the total cases of food allergy. Milk is one of the three commonest food allergens, being second in frequency to wheat and equal in incidence to egg. In a series of 175 cases of food allergy Rowe (1b) found 57% due to wheat, 31% to milk and 35% to egg, the overlapping figures being due to multiple sensitization in some of the patients. Alvarez (2) in a group of 500 cases of abdominal distress due to food allergens found 26% due to milk, cream and ice cream, and another 5% due to cheese. Secondly, its diagnosis can often be made a simple office or bedside one, because (in contrast to the case where egg or wheat are the allergic agents) of the readiness with which milk products can be eliminated from the diet, without necessitating complicated special diets or unusual food preparations. Furthermore, milk products can temporarily be withdrawn without inconvenience to the adult patient, and without interfering with any other diagnostic or therapeutic procedure one may wish to do at the same time. Often the therapeutic test of milk abstinence results in such dramatic relief that the diagnosis becomes obvious while these other procedures are in progress. Repeated periods of ingestion and abstinence then,

with reproduction and relief of symptoms respectively, make the conclusion certain. It goes without saying, of course, that all diagnostic procedures required to rule out a possible organic gastro-intestinal lesion must be carried out.

The symptoms of food allergy as related to the bowel, are most often those of excessive motor and secretory hyperactivity characteristic of the so-called "spastic colon," namely borborygmi, abdominal cramps and diarrhea of watery or mucus stools. However, there are certain symptoms which should especially arouse suspicion of an allergic etiology; to such an extent indeed that they might well be labelled trade marks of food allergy of the bowel. The recurrence of attacks of severe abdominal cramps, due to intestinal spasm, occurring especially shortly after meals, and associated with the explosive expulsion of large mushy or liquid, foul smelling brown to yellow stools, in which round coin-like gobs of mucus float, followed at frequent intervals by further watery evacuations, are especially characteristic. The cramps may be intensely painful, often causing the patient to double up, but where the desire for evacuation cannot be complied with at once, and an intense voluntary effort is made to overcome this desire and keep the anal sphincter closed, the spasm will often subside completely, only to recur after a variable period of minutes with the same or increased intensity; and this may be repeated several times until evacuation finally occurs. Again, a single evacuation though seemingly complete and productive of great temporary relief, is followed by repeated spasms and further liquid evacuations usually of lesser amount until finally the bowel is quieted. With repeated evacuations tenesmus is frequent, and the anal canal feels raw and irritated. Where the ingested irritant is frequently taken, even with every meal, the sense of abdominal discomfort and intestinal unrest is more or less continually present, interspersed with periods of intense spasms described above. Constant daily diarrhea and tenesmus are present, and the sleep is often disturbed several times a night by the characteristic spasmodic cramps and evacuations. A symptom-free interval from the time of arising in the morning to breakfast frequently occurs and is very characteristic; it is due, no doubt, to the period of abstinence from the causative food during sleep. In the more prolonged cases, gross blood may appear in the stool, usually in the form of blood stained or grossly bloody gobs of mucus, and of course this is usually a matter of grave concern to the patient and physician. Where this occurs proctoscopic examination may reveal hemorrhagic spots in the mucosa, or, as in one of the cases here reported, small superficial ulcers.

Where these symptoms are recognized as being suspicious of an allergic colitis, a personal and familial history directed toward other allergic manifestations, such as asthma, hay fever, or food allergy may be confirmatory and illuminating.

The question of the justification for the allergic interpretation of every case of milk intolerance may be raised. May we not be dealing merely with an intolerance due to the presence of substances with cathartic or irritant properties of a pharmacological nature, such as, for instance are commonly assumed to be present in prunes, figs and rhubarb? This objection, however, does not apply with equal force to the case of

milk intolerance, where the experimental and clinical basis for the allergic mechanism has been firmly laid; even to the point of the demonstration of specific sensitivity to certain of the four proteins present in milk, and of the presence of unaltered milk proteins in the blood and urine of sensitized persons, by immunological methods (3). The following clinical observations are also of importance in this connection. There is frequently present a marked personal and familial allergic history. Sensitivity to minute amounts of milk often develops where large amounts had been previously well tolerated. There is often a latent period of sensitization, during which no milk at all may have been taken, between a period of overindulgence and the time of the actual manifestation of symptoms. There may be present a diseased or ulcerated stomach or bowel during the period of sensitization, with a consequently increased permeability of their wall for unchanged milk protein; this combination of ulceration and excessive milk ingestion, as factors in inducing milk sensitivity, is often met with in the treatment of peptic ulcer by the Sippy regime. Occasionally the intolerance develops following parenteral injection of milk. And finally, well recognized allergic symptoms, such as bronchial asthma, hyperesthetic rhinitis, urticaria, migraine, or eczema may appear simultaneously with the gastro-intestinal symptoms following a single milk ingestion. These considerations strongly support the allergic interpretation of milk intolerance, and place the burden of proof on those who question this interpretation.

Case 1. S. R., a lawyer, 30 years of age, gave a history of the sudden development of intestinal symptoms six months previously, following a period of great emotional strain, and shock, considerable alcoholic and dietary indiscretion, and little sleep. These consisted of daily attacks of mild, to excruciatingly severe, spasmodic cramps associated with frequent bowel movements, soft but not watery in character, and such marked urgency of defecation, that the patient would often be forced to abandon his automobile in the middle of a busy street and hurry to a lavatory. He had noticed no relation to the ingestion of any particular food, although the symptoms were aggravated shortly after meals. A symptom-free period usually occurred from the time of awakening in the morning until breakfast. He had seen no mucus or blood in the stools. He had had a complete medical workup elsewhere, which included physical examination, blood Kahn, blood chemistry, complete blood count, urine, basal metabolic rate, electrocardiogram, X-ray of the chest, gastro-intestinal X-ray, Graham Cole visualization of the gall bladder, many stool examinations, and proctoscopic examination of the lower bowel. Of these the only noteworthy findings were: a basal metabolic rate of  $-7$ ,  $-13$ , and  $-17\%$ . The stools had revealed no amoebae or cysts; a ++++ benzidine occurred in many but negative reactions were also reported. The gastro-intestinal X-ray revealed a spastic descending colon. The proctoscopic examination revealed hemorrhagic spots in the mucosa of the rectum and sigmoid. After the routine treatment for "spastic bowel" was of no avail, the patient had been subjected to a series of injections of emetine hydrochloride and had also taken carbarsone by mouth as a therapeutic test for amoebic dysentery, all to no avail. Thyroid extract had also been taken without relief. He was advised to go on a vacation, which he did for a period of five weeks, but returned with the same bowel complaints, although his general health improved.

The symptomatology was highly suspicious of an allergic condition of the bowel. With this in mind the following family history was then available. An uncle (E. R., see

next case) has been found by the present examiner to have a bowel allergy to milk. A niece has asthma and hay fever and has been sensitive to various foods almost from birth. An aunt and cousin have hyperesthetic rhinitis, which in the cousin has been definitely proven to be caused by wheat and citrus fruits. This same cousin after several atypical attacks of right lower quadrant abdominal pains, had an appendectomy; only a peri-appendicitis was found and the appendix was found infiltrated with eosinophiles, on microscopic examination. Another cousin (L. C. below) is also highly sensitive to milk, the ingestion of which causes severe cramps and diarrhea.

Physical examination revealed only a tender sigmoid. An Ewald test meal revealed free acid 50 total 75. A stool was brown, mushy and showed ph. 6.0, faintly positive benzidine test for occult blood, no amoebae, cysts or parasites, 50% Gram + flora, and an occasional meat fibre; a milk culture for the Welch bacillus (a test of value in fermentative diarrhea) was negative.

The daily occurrence of the symptoms suggested that some common allergen was at fault. Because it was the easiest to eliminate from the diet, milk and dairy products were completely prohibited temporarily. The symptoms immediately disappeared, and after six months of almost daily distress the patient at once experienced dramatic relief. Repeated trial of ingestion of milk always caused recurrence of the trouble, abstinence always caused complete relief, thus leaving no doubt as to the etiology of the condition.

Case 2. E. R. (an uncle of patient presented as Case 1) 35 years old, was seen in 1934 complaining of occasional heartburn and belching, not relieved by soda, for 15 years. He passed much flatus. Two days previously he had ingested a chocolate bar and a glass of milk, and the rest of the day had severe cramps and diarrhea. On the day of examination he felt well. Examination revealed only a distended and tympanitic abdomen. Stool examination revealed nothing pertinent, and a gastro-intestinal X-ray examination was refused at the time. Abstinence from milk relieved all symptoms.

He was seen again in 1937 at which time he complained of a recurrence of generalized spasmodic attacks of abdominal cramps associated with loose stools containing mucus but no blood. On awakening in the morning he felt well, but symptoms occurred soon after breakfast. He stated that milk acted as a cathartic on him, and he had been avoiding it since last seen, but he ate butter, sweet cream and cheese. Examination again revealed only a distended tympanitic abdomen. A gastro-intestinal X-ray study revealed only a spastic descending colon. He was advised to eliminate all dairy products temporarily. All symptoms immediately disappeared. By subsequent trial and error he found that if in addition to milk he avoided also cheese and cream and ate only minimal amounts of butter he was symptom free. With these restrictions he has been symptom free since. He has been supplied with a source of Vitamin A and calcium.

Case 3. S. J., a man 44 years old, was seen at his home where he was bedridden with abdominal cramps, occasional diarrhea, and vomiting. His symptoms dated back one month, when because of gastro-intestinal upset he had been placed on a milk and cream diet. Various diagnostic measures and treatments having been to no avail, an appendectomy had been advised, and in expectation of this the patient had cancelled a position which he had been about to accept in a distant city. Examination revealed an anxious individual with moderate abdominal distension, and with a generally tender colon. On being questioned about his diet, the patient stated that because of his abdominal complaints his medical advisers had prohibited anything but milk and cream. On further questioning as to previous effects of milk he stated that he had habitually used milk as a cathartic. The patient was advised that

stopping his "cathartic" might cause his cramps to disappear, and indeed such proved to be the case. The patient left the city to take the position which had been offered him. In a letter four months later he stated that he had no symptoms as long as he avoided milk. Ingestion of milk always causes recurrences of his symptoms.

Case 4. L. C., a man 30 years of age, presented a more or less typical history of a duodenal ulcer which was confirmed on X-ray examination. Symptoms were relieved on the Sippy diet with hourly milk and cream feedings. However, severe spasmodic abdominal cramps and diarrhea, often explosive in nature, of soft to watery stools containing gobs of mucus, occurred almost daily, and often at night, disturbing the patient's rest. Grossly bloody gobs of mucus began to appear. Gastro-intestinal X-ray examination revealed the duodenal lesion, spastic colon, and a spasm of the cecum which at first was considered to be an organic lesion; exploratory laparotomy was advised but refused. Proctoscopic examination revealed two superficial tiny ulcers in the rectum. Cultures and smears were negative for amoebae or other infectious agents. After several months of these symptoms the patient stopped taking milk and cream, with immediate and dramatic cessation of his colonic symptoms. By trial and error it was subsequently found that he could tolerate small amounts of butter, cream and cheese but ingestion of milk always caused intense abdominal cramps and diarrhea. He also discovered that raw apple, tomato and peach reproduced the symptoms even if minute amounts of these foods were taken. Five years later the patient is well nourished and symptom free, as long as he avoids the food he knows he is allergic to. The stool contains no occult blood.

Case 5. Mrs. L. B. was known to have chronic rheumatic heart disease and mitral stenosis for at least the past 15 years. For the past two years she had been bedridden because of fatigue and dyspnea on exertion, incidental to marked pulmonary passive congestion. Congestion of the abdominal viscera caused marked dyspepsia, so that the patient voluntarily restricted her diet mainly to milk. For the past four weeks she had been experiencing abdominal cramps which occurred only after meals and were absent in the morning before breakfast. At first these were considered as being another evidence of the dyspepsia due to the passive congestion of the viscera, until the predominant role of milk in the patient's diet was realized. As a therapeutic test, milk was stopped, and a mixture of cream and water was substituted. The symptoms disappeared, but the patient so missed her milk that she frequently returned to it, each time with recurrence of cramps, so that she was herself finally convinced of the association, and stopped the use of milk completely.

#### COMMENT

The bedside character of the diagnosis, as well as the method of arriving at it, are well illustrated in these cases. It is necessary to constantly keep in mind the frequency of milk allergy of the bowel, and to be on the alert to recognize the symptoms which characterize it. The suspicion of its presence may be strengthened by a careful investigation of the history for personal or familial allergic manifestations. This suspicion however slight, may then be readily confirmed or disproved, by merely prohibiting the use of milk and milk products for a period of several days; in most cases relief of symptoms is experienced within twelve hours, but the period of abstinence should be prolonged to several days for certainty. Elimination of milk products can usually be accomplished without hardship to the patient, but where for certain reasons milk forms the greater part of the diet and the patient is not sympathetic to its removal, it may be necessary to compromise by substituting a mixture of cream and

water. This is effective where the sensitivity to milk is relatively mild so that the small amount of soluble milk proteins remaining in the cream is not sufficient to cause symptoms. The relief of symptoms by the withdrawal of milk, and their reproduction by its ingestion confirms the diagnosis clinically. The paraphernalia of the allergist, valuable as these may be elsewhere, are here completely dispensed with.

The frequency and importance of the symptom-free interval before breakfast in the diagnosis of food allergy of the bowel has already been mentioned and is well illustrated in the case histories presented; to my knowledge it has not previously been stressed elsewhere. From the explanation given for its occurrence (namely that is due to the period of abstinence from the irritating food during sleep) it is apparent that it may not be invariably present, even in the same individual. A transient period of heightened susceptibility, or an unusually large dose of the allergen taken the previous evening, may cause persistence of symptoms through the next morning even in the period before breakfast. Nevertheless the occurrence of this matinal symptom-free interval is highly characteristic.

The interpretation of the results of the withdrawal and ingestion of milk products depends to a certain degree on a knowledge of certain peculiarities of milk sensitivity. These peculiarities also determine how drastic the elimination of milk and its derivatives shall be therapeutically, in a case where the diagnosis is established.

The degree of sensitivity varies. The most highly sensitive individuals do not tolerate the minute amounts of the soluble milk proteins present in cream, cheese, and even butter which contains the least. Patients with a lesser degree of sensitivity may tolerate small amounts of cream, cheese and butter, while others may tolerate butter, but not cheese or cream. The least sensitive patients may take boiled, evaporated, or dried milks, and some even small quantities of raw milk and ice creams containing milk. One form of cheese may be well tolerated in a given individual and another cause the characteristic symptoms, presumably due to differences in methods of manufacture, degree of washing and aging. The irritation produced by milk may in a few cases be a cumulative one; one ingestion of milk may be innocuous but repeated daily intake may produce a degree of irritation of the bowel which prohibits even a lesser amount of milk than could be tolerated at the outset.

The length of the period after a single intake of milk before symptoms appear is variable and inversely proportional to the degree of sensitivity and the amount of milk consumed; symptoms may appear within a few minutes or may be delayed for 12 to 24 hours. The duration of symptoms following a single ingestion is likewise variable and directly proportional to the degree of sensitivity and the amount of allergen ingested; it may vary from one or two to 24 or 36 hours. Where the bowel is already irritable for any reason, for instance, because of the recent consumption of another allergen or some other type of irritant, it may then prove intolerant to an amount of milk ordinarily well tolerated. The theoretical basis of the entire subject of milk sensitivity is treated in detail in the fundamental contribution of Ratner (3); the question of the possibility of direct sensitivity to the



insoluble protein, casein, is taken up in his paper and in the discussion which follows it.

In Case 4 the point is illustrated that the elimination of the more serious offending food, with relief of the chronic gastro-intestinal distress, permits the discovery of less commonly ingested irritants, by the more sporadic character of the abdominal symptoms they elicit, because of their less frequent occurrence in the diet. Indeed, the patient once having been made allergy conscious will himself look for and discover foods that he cannot tolerate. This of course occurs more or less commonly where no medical advice has been sought for. Many lay people come to the physician with the information that this or that food does not agree with them. It is well to remember that the most succinct and ancient definition of allergy—"one man's meat is another man's poison" (definitely implying individual idiosyncrasy)—was probably formulated not by a physician but by a lay person.

The symptoms due to milk allergy may arise accidentally, as illustrated in Case 5, in the course of some chronic disease which may itself be characterized at times by the same type of symptoms, so that these are interpreted as being due to the basic disease, and the true state of affairs, namely a coincidental development of allergy to milk, remains obscure for a long time, and may never be recognized. Mackie (4) has recently reported cases of chronic ulcerative colitis in which symptoms of pain, diarrhea and bleeding were ameliorated by the withdrawal of milk from the diet and aggravated by its ingestion. Two interpretations are implied. The constant irritation of an unrecognized milk allergy might lead to a state of chronic bowel ulceration; this is, at present, a matter of some speculation. The state of milk allergy may be accidentally superimposed on and help perpetuate a chronic ulcerative colitis; this view would seem, as yet, to be the one more readily to be accepted, and would place these cases in the same category as that of the last case here reported, namely a functional bowel disturbance superimposed on a chronic organic disease, in this case of the bowel itself.

It is interesting to note the occurrence of milk allergy of the bowel in three members of one family,

in this series of cases. However, in several other highly allergic members of the same family, (cited in Case 1), allergy to milk is not at all present.

### SUMMARY AND CONCLUSIONS

1. Food allergy is a more common cause of functional bowel disturbance and spastic colon than is generally appreciated.

2. Milk is one of the more common allergens responsible for such colonic food allergy, accounting for about 25% of the cases.

3. Milk allergy can be more readily recognized or excluded by simple trial and error method than other common food allergens (e.g. wheat or egg) because it is more easily eliminated from the diet. The diagnosis therefore may often be made a simple office or bedside one.

4. A symptom-free interval, in the period between arising in the morning and the ingestion of breakfast, frequently occurs, and is of importance in the diagnosis of colonic food allergy.

5. The recognition of the allergic nature of certain bowel disturbances, may prevent serious diagnostic errors, and unnecessary, often dangerous, medical and surgical procedures.

6. The physician should be "allergy conscious," in his investigation of obscure bowel disturbances.

7. Organic disease of the gastro-intestinal tract should always be ruled out by appropriate diagnostic procedures; however, organic disease and allergic functional disturbance may coexist.

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## Studies in Human Biliary Physiology

### V. Influence of Metabolizable and Non-Metabolizable Sugars on Liver Bile Secretion\*

By

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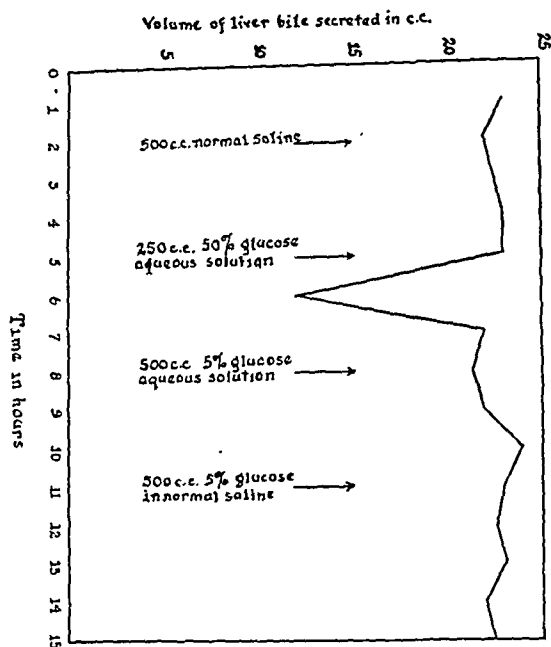
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IN previous papers (1, 2), we have shown that the quantity of bile secreted through a total external biliary fistula by a cholecystectomized healthy female having an apparently normal liver remains constant and can be reproduced at will under basic conditions. It was further shown that orally administered high

carbohydrate diet did not apparently stimulate bile secretion when no bile was returned to the patient. When bile was returned, there still was no increase in bile secretion that could be interpreted as due to the carbohydrate of the diet.

Inasmuch as the intravenous administration of glucose and saline solutions is a very widely used surgical therapeutic procedure, and is also used in a wide variety of non-surgical diseases, especially in-

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Graph 1. Effect of intravenous saline and glucose on secretion of liver bile. Note sharp depression in bile flow induced by 125 gms. of glucose (50% solution), with return to starvation level in 2 hours after injection. The other solutions had no effect on bile secretion.

volving the liver, it was deemed advisable to determine the effects of such solutions on the hourly flow of bile in our subject. The most commonly used solutions are normal saline, 5% glucose in normal saline, 5% aqueous solution of glucose, and 50% aqueous glucose. These solutions were used in the quantity ordinarily employed in practice.

**Procedure.** At the time of the experiments, the patient weighed 56.3 kgs. As in previous experiments, the patient's food intake was progressively decreased for a week prior to the experimental test day. No food whatever was administered on the day before the test day nor on the test day. A small amount of water was allowed by mouth. On the test day, the bile was collected at hourly intervals for three one hour periods. The following solutions were then injected intravenously: 500 cc. normal saline (osmotic pressure 3.5A), 500 cc. 5% aqueous glucose (osmotic pressure 61.7A), 250 cc. 50% glucose (osmotic pressure 6.1A), and 500 cc. 5% glucose in normal saline. In each instance the fistula bile was collected hourly for at least three hours following the injection, or until the bile flow had returned to the fasting level and remained at that level for at least one hour after it had reached that point, before another solution was administered. These injections were repeated, after a preliminary preparatory period as outlined, on five different test days, the order of injection of the solutions being varied on each occasion. Such variation did not affect the quantity or rate of bile secreted. The results of a typical test day are recorded in Chart 1.

It can readily be seen from the graph that neither

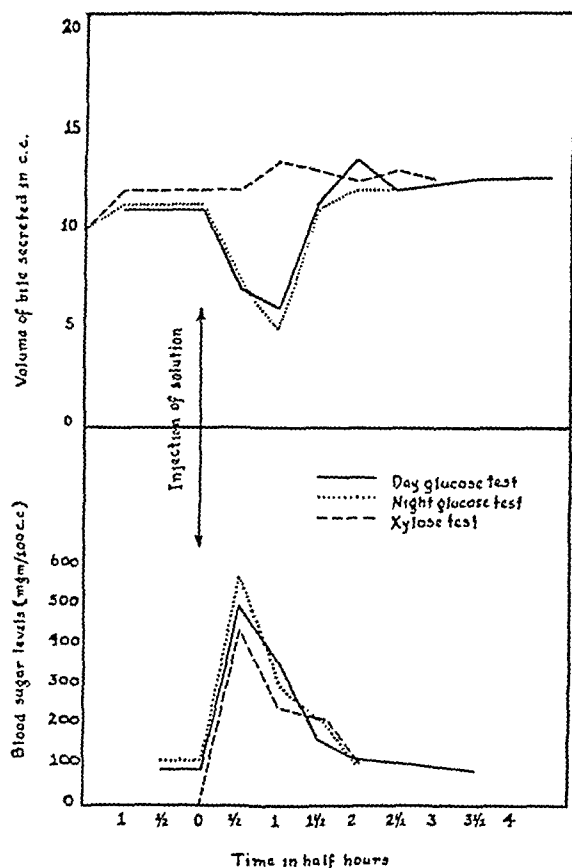
normal saline nor 5% aqueous glucose or glucose in saline, used in 500 cc. quantities as is usual in single-injection surgical practice, has any effect upon the rate or quantity of bile secretion. The administration of a 50% glucose solution, however, depresses the quantity of bile secreted by about fifty per cent in about one hour from the time of injection, the bile flow returning to the fasting level in two hours from the injection and remaining thereafter at this level.

From these experiments it appeared that the only factor altered that might explain the depression in bile flow noted with the 50% glucose was the total quantity of glucose administered. Woodyatt, Sansum and Wilder (3) had shown that 63 grams of glucose, intravenously injected, could be absorbed by a man of 70 kilograms without resulting glycosuria. In our experiments, glycosuria did not appear when 25 grams of glucose (5% solution) were injected, but did appear when 125 grams (50% solution) were given. It was postulated by us, then, that the glycogenetic function of the liver had been overloaded and that thereby its bile-producing function had been depressed. That a reciprocal relation between these two functions exists was suggested, on anatomical grounds, by Forsgren (4). If this were the mechanism involved in the depression of bile flow noted in our experiments, it was further postulated that the intravenous injection of a non-metabolizable sugar, such as xylose, which, so far as is known, cannot be stored in the human body (5), should cause no change in the quantity or rate of bile secretion. The following experiments were carried out on our patient to test these postulates, as well as to note the diurnal cyclic bile-glycogen forming relationship suggested by Forsgren (4).

**Procedure.** After a preparatory starvation period as in our previous experiments, the bile was collected from the fistula at two or three half-hourly intervals. A blood sugar determination (Folin-Wu method) was done, following which 250 cc. of 50% aqueous solution of glucose (125 gms.) was injected intravenously, the injection being begun at 10:30 a. m. and being completed at 10:50 a. m. At half hourly intervals from 10:30 a. m. the fistula bile was collected and measured, the urinary bladder was completely emptied per catheter, and venous blood was taken for blood glucose determination. Quantitative urinary glucose determinations were made on the individual specimens.

Again, on another test day, after similar preparation, 250 cc. of 50% aqueous solution of glucose was intravenously injected, the injection being begun at 10:30 p. m. and being completed at 10:50 p. m. Similar bile, blood and urine determinations as in the previous experiment were made.

On still another test day, after similar preparation as above, 250 cc. of 50% aqueous solutions of xylose (C. P.—Eimer & Amend Co., New York City) was injected intravenously at 10:30 a. m. Bile, blood and urine determinations were made, the sugar determinations in this instance being those for xylose by the method of Folin and Svedberg (6) as modified by Somogyi (7) and Hiller, Linder and Van Slyke (8). Pre-injection blood and urine glucose determinations were performed.



Graph 2. Effect on bile secretion and relation to blood sugar or blood xylose level produced by intravenous injection of 125 gm. of glucose at mid-day (solid line) and at midnight (dotted line) and by 125 gm. of xylose (broken line). Note that xylose has no effect on bile secretion and that a similar amount of glucose depresses bile flow by about 50% regardless of time of administration. Note also the peak of the blood sugar curves half hour before the maximal depression of bile flow.

In the case of the xylose experiment, the blood sugar curve represents xylose values, in the others glucose. (See Tables I, II, III).

The results of these determinations are recorded in Tables I, II and III, and graphically in Chart 2.

### DISCUSSION

It has been suggested in recent years that a relationship exists between the glycemic function of the liver and biliary tract disease (9). It has further been shown that the blood glucose level can be altered experimentally in animals by the injection of bile salts or acids (10, 11), and that glycogen formation by the liver can be enhanced by the oral administration of bile salts (12). So far as we could find, the only suggestion that bile flow can be modified under the influence of glucose injections was made by Kocour and Ivy (13), who, like ourselves, found that the intravenous injection of hypertonic glucose solution depressed the flow of fistula bile in a cholecystectomized dog. While the concentration of the individual injections used by them was definitely lesser than ours (17.5% as against 50%), it will be noted by reference to Table VIII (cols. 3 and 4, 9 and 10) of their paper

TABLE I

*Fistula bile, blood and urine glucose determinations on patient given 250 cc. of 50% glucose intravenously at 10:30 a. m.*

Time of Injection	Fistula Bile in cc.	Blood Sugar (mgm./100 cc.)	Urine		
			cc.	% Glucose	gm. Glucose
Pre-injection (1½ hr. intervals)	11, 11	95	100	0	0
¼ hr. post-injection	7	500			
1 hr. post-injection	6	360	160	5.5	8.8
1½ hr. post-injection	11.2	170			
2 hr. post-injection	13.4	131	635	3.1	19.7
2½ hr. post-injection	12.0		70	1.5	1.0
3½ hr. post-injection	12.5	92	35	v.f.t.	
4½ hr. post-injection	12.5		30	0	0

that only after the third such injection had been given (35 grams of glucose being given at each injection) did the bile flow diminish materially. These results suggest that in their experiments, as in ours, the quantity of glucose administered rather than its concentration in the injection is the factor responsible for the bile flow depression noted by them.

Similarly, the discrepancy between the duration of depression in bile flow found by Kocour and Ivy, and by us, is more apparent than real. Examination of the above mentioned table shows that, from the time depression was noted, 18 hours elapsed until the return to the normal bile flow (cols. 9 and 10). In this instance, 105 grams of glucose had been administered to a dog of 11 kilos. Assuming the figures of Woodyatt, Sansum and Wilder (3) to hold for dogs, this dog could have received 9.9 grams of glucose without resulting glycosuria. Compared, then, with the overload in our experiments (in which the absorbable amount of glucose was slightly more than doubled in relation

TABLE III

*Fistula bile, blood and urine xylose determination on patient given 250 cc. of 50% xylose intravenously at 10:30 a. m.*

Time of Injection	Fistula Bile in cc.	Blood Xylose (mgm./100 cc.)	Urine		
			cc.	% Xylose	gm. Xylose
Pre-injection (1½ hr. intervals)	10, 12, 12	0	85	0	0
¼ hr. post-injection	12.0	440	60	2.5	1.5
1 hr. post-injection	13.5	250	85	4.0	3.4
1½ hr. post-injection	13.0	222	260	5.0	15.0
2 hr. post-injection	12.5	105	127	4.5	5.7
2½ hr. post-injection	13.0				

to the patient's weight), it is probable that a glycemic level was established by them which might, in effect, act as a continuous source of available glucose of sufficient amount continuously to stimulate the glycogenic function of the liver and depress its bile forming ability. Reference to columns 3 and 4 of the same table seems to bear out this possibility. In this dog 105 grams of glucose were administered before the bile flow was depressed. An additional 35 grams was then injected. In spite of this procedure, the bile flow returned to the preinjection level in 18 hours after the glucose administration had been discontinued. In this dog, also, the glucose overload, compared with that in our case was, if one injection alone relative to weight is considered, as 4.1 is to 2.6; and, if the total quantity of glucose injected relative to the weight of the subject is the basis of comparison, it was 7.1 to 1. i.e.,  $\frac{140 \text{ gms. glucose}}{11 \text{ kgms.}}$  and  $\frac{125 \text{ gms. glucose}}{56.3 \text{ kgms.}}$ . Since in our experiments the depression of bile flow lasted some two hours with a single injection, it is not surprising for

TABLE II

*Fistula bile, blood and urine glucose determination on patient given 250 cc. of 50% glucose intravenously at 10:30 p. m.*

Time of Injection	Fistula Bile in cc.	Blood Sugar (mgm./100 cc.)	Urine		
			cc.	% Glucose	gm. Glucose
Pre-injection (½ hr. intervals)	10, 11, 11	112	75	0	0
½ hr. post-injection	7	571	700	5.5	38.5
1 hr. post-injection	5	312	100	5.6	5.6
1½ hr. post-injection	11	228	25	4.5	1.1
2 hr. post-injection	12	108	20	3.8	0.7
2½ hr. post-injection	12		5	2.9	0.1

Kocour and Ivy, working with repeated injections, to have obtained a depression of bile flow lasting constantly some 18 hours.

As in their results, we found no bile flow depressive effects attributable to the water content of the solutions injected, nor were we able to note any depression with changes in the osmotic pressures of the fluids administered or by the use of an electrolyte in the injection medium. That the depression in the bile flow was entirely attributable to an overload of the glycogenic function of the liver is indicated, we believe, by the complete absence of such an effect when a solution of a non-metabolizable sugar, xylose, was injected identical in amount and concentration to that of the glucose solution giving rise to the depression noted. Parenthetically it may be noted that there were no untoward local or systemic effects as the results of the xylose injection.

Our results further indicate that the rhythmic diurnal reciprocal relation between the glycogenic and bile secretory functions of the liver suggested by Fors-

gren (4), Holmgren (14) and Agren, Wilander and Jorpes (15) does not obtain, in the human, under strictly basal conditions. We were able quite as readily to depress the flow of bile at midnight when, according to Forsgren, the glycogenic function should have been at its height and the glycogen content of the liver highest, as we were at noon when its glycogenic function should have been at its ebb, the glycogen content of the liver lowest, its bile content maximal. The difference in the amount of glucose excreted in the urine during the night test (46.0 grams) and that excreted during the day glucose test (28.5 grams) may be due to the unavoidably greater activity of the patient during her waking hours by day, even though in bed, and the consequent utilization of the 17.5 grams of glucose.

Our experiments, as well as those of Kocour and Ivy, indicate that the depression in bile flow following the intravenous injection of glucose is a real, if transitory, phenomenon if solutions of sufficient concentration to overload the liver with their glucose content are used. Such solutions should be used with some caution where it is desired to maintain an uninterrupted flow of bile, as in post-choledochostomy cases, as well as in cases of liver disease with already depressed biliary function.

## SUMMARY

1. Intravenous injection of hypertonic 50% glucose solution depresses the flow of fistula bile in a cholecystectomized individual. This depression is due to the large amount of glucose injected, with a consequent overload of the glycogenic function of the liver. It is not due to the concentration itself.

2. Intravenous injection of a non-metabolizable sugar in amount and concentration identical with that of glucose causing a depression of flow of fistula bile brings about no such depression.

3. It is suggested that glycogenic and bile secretory functions of the liver are reciprocally inter-related. This inter-relationship is not influenced in man by diurnal variations under basic conditions.

4. It is suggested that large amounts of intravenous glucose be used with caution in cases of liver disease with already altered biliary function and in such cases in which it is desirable to maintain continued post-operative secretion.

5. Neither the water content nor the osmotic pressure of intravenously injected solutions as ordinarily utilized in clinical practice affects the flow of fistula bile.

6. The presence of an electrolyte (isotonic saline) in a glucose solution does not affect liver bile secretion.

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## Secretory Studies in Whole Stomachs The Dilution Indicator Technique and its Precision Measures\*

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A DILUTION INDICATOR in gastric analysis is a substance incorporated into the test-meal in known concentration for the purpose of determining quantitatively the proportions of secretion and test-meal present in each sample of gastric contents. The ratio of the indicator concentration in each sample to that in the test-meal itself yields the proportionate volume of the latter in the sample in question (see equation (1) below). By means of these proportions the *observed acid and chloride concentration values* for each specimen (i.e., the values commonly reported in gastric analyses) can be converted to *corrected values*, which represent the respective concentrations in the mixed secretion undiluted by the test-meal. A dilution indicator can be similarly employed in gastric pouch experiments to study absorption or ionic interchange across the mucosa, as well as secretory phenomena. In our laboratory it has already proved to be valuable in demonstrating the occurrence of fluid absorption in the unoperated stomach. A similar technique is being used by Visscher (1940) in his studies on intestinal absorption in which the dilution indicator (or reference substance, as he calls it) is  $\text{Na}_2\text{SO}_4$ . Since the time when Mathieu (1896) first employed an emulsion of oil and gum in a test-meal of bread and tea, many substances have been used as dilution indicators, but none of them found wide acceptance until Lanz (1921) introduced phenolphthalein. Two years later Gorham (1923) published experiments in which he used phenol red (phenolsulfonphthalein) for this same purpose. Since then, there have been reported a considerable number of clinical and experimental investigations based on one or the other of these dilution indicators; of these the most recent and extensive is contained in the series of papers by Wilhelmj and his associates (e.g., Wilhelmj, Neigus and Hill, 1933; Wilhelmj, Finegan and Baca, 1939).

To be suitable for use as a dilution indicator, a substance must be (1) nontoxic, (2) not absorbed in the stomach, (3) not destroyed, precipitated, nor absorbed by any constituent of the stomach contents, (4) of such a nature as not to interfere with acidity or other determinations, and (5) capable of analytical determination by a relatively simple procedure with a precision of at least one per cent. Of all the many substances which have been employed for this purpose, only phenolphthalein and phenol red have been used at all extensively, a fact which must be ascribed to the failure of all the others to meet the foregoing conditions. Even phenolphthalein, which seemed for a time to be better suited for the purpose than any other

substance, proved to be unsatisfactory because a considerable amount of it precipitates out of the test-meal when the latter is introduced into the stomach (Hollander, Penner and Saltzman, 1937).

Thus, of all the substances investigated, only phenol red is suitable as a dilution indicator. That it does not undergo gastric absorption in the dog was suggested by Wilhelmj *et al* (1933) on the basis of some indirect evidence; they also demonstrated that the indicator undergoes no chemical change *in vitro* when incubated with bile or with gastric juice at 37° C. for periods of six to forty-eight hours. In humans, we were able to demonstrate directly on the unoperated subject that there is no loss of phenol red from the stomach (either normal or diseased) in any way except by passage with the gastric contents into the duodenum (Penner, Hollander and Saltzman, 1938); this has recently been confirmed by Shay, Gershon-Cohen and Fels (1939). The duration of these latter observations was as long as a test-meal usually remains in the stomach, a maximum of three hours. Since it is our practice to use phenol red as a titrimetric indicator for total acidity, its use as a dilution indicator does not interfere with subsequent analytical procedures. Finally, we have developed a method of suitable reliability and simplicity for the analytical determination of phenol red in the presence of bile and protein suspensions (Hollander and Penner, 1940). Hence, this substance satisfies all of the prerequisites for a dilution indicator enumerated above and there is no reason apparent at this time for its not being used either in fractional gastric analyses or in experiments involving fluid retention in isolated stomach pouches. Its use in intestinal experiments, however, is precluded by its absorbability in this portion of the digestive tract.

In the course of our work with the dilution indicator method it has become apparent that, under certain conditions, the experimental errors of the several analytical procedures employed in this technique may be compounded in such a way as to yield errors of considerable magnitude in the final *corrected concentrations*. This may occur even though the reliability of the individual analytical methods (expressed as standard error) is never worse than 2 m.eq. per liter for the chloride and acidity titrations, nor 0.4 mg. per liter for the phenol red. Such a compounding of analytical errors arises entirely from the arithmetical manipulation of the data and is inherent in the dilution indicator technique itself. None of the previous workers appear to have been cognizant of these magnified errors, since we have been unable to find any mention of them in the literature. Consequently,

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we are presenting a mathematical analysis of these several errors and a set of graphs to indicate their actual magnitudes under a variety of experimental conditions.

### FORMULAE AND ERROR EQUATIONS

Let  $P_i$  and  $C_i$  = the concentrations of phenol red and chloride (or acid) respectively in the test-meal (hereafter called the *initial concentration*); these are treated as parameters throughout.

$P_o$  and  $C_o$  = the concentrations of phenol red and chloride (or acid) respectively in any gastric sample (hereafter called the *observed concentration*).

$C_c$  = the concentration of chloride (or acid) corrected for test-meal dilution, i.e., the calculated concentration in the mixed secretion without the test-meal (hereafter called the *corrected concentration*).

$f_i$  and  $f_s$  = the proportions by volume of test-meal and mixed secretion respectively in the gastric sample; i.e.,  $f_i + f_s = 1$ .

$\pi$  and  $\epsilon$  = the precision measures of the analytical procedures for phenol red and chloride (or acid) respectively, determined as standard errors\* and expressed in units of concentration. These may be defined as the differentials of  $P_o$  and  $C_o$  respectively, i.e., ( $dP_o$ ) and ( $dC_o$ ).

[E:] = the experimental error in any calculated value, and is defined as the differential of this value. The nature of the calculated value is indicated by a suitable symbol following the colon inside the bracket; the analytical error causing [E:] is indicated by a superscript outside the bracket.

Now, the values which are usually calculated in the course of an experiment are given by the following equations (see Addendum I for their derivation):

$$f_i = \frac{P_o}{P_i} \quad (1)$$

$$f_s = \frac{P_i - P_o}{P_i} \quad (2)$$

$$C_c = \frac{C_o - C_i f_i}{f_s} \quad (3)$$

In a special situation where the test-meal contains none of the secretory constituent being investigated,  $C_i = 0$  and (3) becomes

$$C_c = \frac{C_o}{f_s} \quad (3a)$$

These equations are actually the formulae employed in our routine calculations of  $f_i$ ,  $f_s$ , and  $C_c$ . The corresponding error equations, i.e., formulae for the various [E:] -values, can now be derived from these equations and the definition of [E:]. The results of such derivations (see Addendum II) are as follows:

$$[E:f_i] = \frac{\pi}{P_i} \quad \text{or} \quad \frac{100\pi}{P_i(1-f_i)} \quad (\text{as per cent}) \quad (4), (4a)$$

$$[E:f_s] = \frac{\pi}{P_i} \quad \text{or} \quad \frac{100}{P_i f_s} \quad (\text{as per cent}) \quad (5), (5a)$$

which measure the errors in the proportions of test-meal and of secretion due to the error in the phenol red determination, and are expressed in terms of these proportions (and also the percentage errors, which are

\*Ordinarily, the standard deviation (which is actually a plus or minus value) is written without regard to sign. In formulating our precision measures, which are all expressed as standard deviation, this same practice has been followed.

particularly useful when  $f_i$  is used to calculate the volume of secretion contained in any sample of gastric contents). Also,

$$[E:C_c] = \frac{1}{f_s} \sqrt{\epsilon^2 + \pi^2 \left( \frac{C_o - C_i}{P_i f_s} \right)^2} \quad (6)$$

which represents the total error in any corrected concentration value ( $C_c$ ) caused by the errors in determination of chloride (or acid) and phenol red concentrations. The values yielded by equation (6) are expressed in terms of the same concentration unit as that employed for the corresponding  $C_o$ -value. In the following analysis of the [E:] -values it must be remembered that each of these corresponds to the standard deviation for a single determination of the derived function.

### RELIABILITY OF THE ANALYTICAL PROCEDURES INVOLVED IN THE DILUTION INDICATOR METHOD

In order to utilize equations (4) through (6) in estimating the reliability of the several calculated values, it is essential that we possess precision measures of the analytical procedures for determining phenol red, chloride and acid concentration (i.e., for  $\pi$  and  $\epsilon$ ). Such precision measures are variously estimated in terms of average deviation, probable error, standard deviation, or range—all of which may be calculated from the actual errors observed in a series of determinations on solutions of known concentration. In the investigation of which this is a part, consistent use has been made of the standard deviation for a single determination (i.e., of the entire distribution) represented by  $\sigma$ .

For the errors in the phenol red method, it has already been shown (Hollander and Penner, 1940) that  $\sigma$  is 0.22 mg. per liter for a test-meal concentration of 40 mg. per liter. This was calculated from a series of 108 determinations on phenol red solutions which contained either egg albumen, gastric pouch juice, Liebig's extract, or human stomach contents with varying amounts of mucus, acid and bile. The phenol red concentration varied from 40 to 0.5 mg. per liter, which covers the entire range likely to be encountered in actual experiment. In order to evaluate the reliability of the acid (Hollander, 1931) and chloride (Wilson and Ball, 1928) titration methods, we performed a suitable number of such determinations on standard HCl (0.1 N). For 40 acidity titrations,  $\sigma$  was 0.9 m.eq. per liter, and there is no reason for believing that it would be significantly different for acid solutions of different concentration. Likewise, for 50 chloride determinations on standard HCl (0.1 N)  $\sigma$  was found to be 0.9 m.eq. per liter.

### EVALUATION OF THE PRECISION MEASURES OF THE DILUTION INDICATOR TECHNIQUE

Let us now consider the magnitudes of the several errors defined by equations (4), (5) and (6). In the foregoing section it has been shown that  $\pi = 0.22$  mg. per liter and  $\epsilon = 0.9$  m.eq. per liter, for both acid and chloride. Throughout all our experiments, the concentration of phenol red in the test-meal ( $P_i$ ) was fixed at 40 mg. per liter. The test-meal concentration of chloride or acid ( $C_i$ ), on the other hand, is a constant for any one experiment or series of experiments,

but its value may change from one series to another.

The errors in the proportions of test-meal and secretion in any sample caused by the error in phenol red determination ( $[E:f,]\pi$  and  $[E:f,]\pi$  respectively) are given by equations (4) and (5). Since  $\pi$  and  $P$  are both constants, these  $[E:]$ -values are also constant and equal to 0.0055, independently of variations in composition of the gastric sample (i.e., in  $f$ ). The

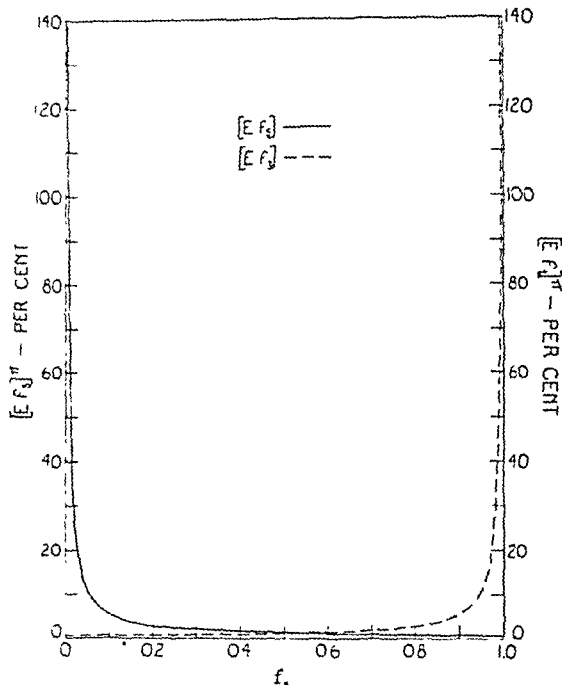


Fig. 1

units of these precision measures are the same as those of  $f$ , and  $f_s$ . However, in order to express them as per cent—which is necessary when  $f_s$  is used to estimate the volume-rate of secretion—equations (4a) and (5a) must be employed. These  $[E:]$ -values are functions of  $f$ , and of  $f_s = (1 - f_s)$  respectively, and the curves of Fig. 1 illustrate the relations among these several variables. It will be noted that  $[E:f,]\pi$  is less than 1 per cent only when  $f$  is greater than 0.55, and it becomes as great as 11 per cent for  $f_s = 0.05$ ; thereafter, the error increases asymptotically. The values for  $[E:f,]\pi$  are analogous to those for  $[E:f,]\pi$  and are also indicated in Fig. 1.

The precision measure for the corrected concentration of chloride (or acid), represented by  $[E:C_s]\pi$ , is dependent upon the reliabilities of the analytical procedures for both chloride (or acid) and phenol red, according to equation (6). This relation for the total error, however, is derived from the two partial errors, (6a) and (6b)—as shown in Addendum II. One of these,  $[E:C_s]\pi$  representing the influence of the chloride (or acidity) determination, is inversely proportional to  $f$ , but entirely independent of  $C_s$ ,  $C_a$ , and  $C$  itself (graphic illustration of these partial errors has been omitted). The minimum  $[E:C_s]\pi$ -value, corresponding to pure secretion ( $f_s = 1.0$ ), is 0.9 m.eq. per liter. The values increase hyperbolically, becoming 3 m.eq. per liter for  $f_s = 0.30$ , 9 m.eq. per liter for  $f_s = 0.10$ , and 18 m.eq. per liter for  $f_s = 0.05$ . The other

partial error,  $[E:C_s]\pi$  representing the influence of the error in phenol red determination, is a function not only of the variable  $f$ , but also of  $C_s$  and  $C_i$ ; actually it is directly proportional to the difference  $(C_s - C_i)$ . Hence, graphic illustration of this relation for  $[E:C_s]\pi$  as a function of  $f$ , can be given by a family of curves, each one of which corresponds to a different set of values for  $C_s$  and  $C_i$ . In all these curves the  $[E:]$ -values are minimal (0 to 1 m.eq. per liter) for  $f_s = 1.0$  and increase asymptotically as  $f$  approaches zero.

The total error in  $C_s$  ( $[E:C_s]\pi$ ), indicated by equation (6), involves all of the variables and constants which enter into the two partial errors. Hence, as in the case of  $[E:C_s]\pi$ ,  $[E:C_s]\pi$  as a function of  $f$ , can be represented by a family of curves for all values of  $C_s$  and  $C_i$ . Since the equation involves the latter in the form of the square of their difference  $(C_s - C_i)^2$ , its graphic representation can be simplified by letting each curve of the family correspond to a different value of  $\pm (C_s - C_i)$ . This has been done in Fig. 2, where the four illustrative curves correspond to the arbitrarily chosen values for  $\pm (C_s - C_i)$  of 0, 50, 105 and 165 respectively. Thus, each of these curves represents an infinity of  $C_i$ -values and an infinity of corresponding  $C_s$ -values, such that their difference is one of the foregoing values for  $\pm (C_s - C_i)$ . Much of our work with the dilution indicator

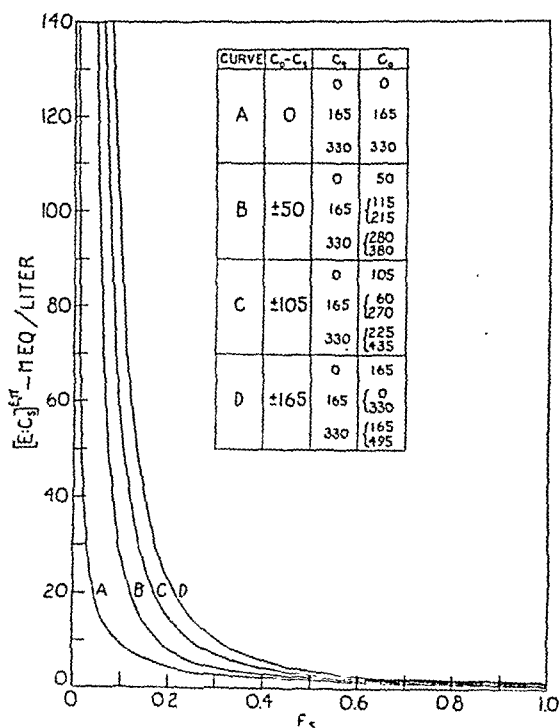


Fig. 2

technique is concerned with test-meals of water, isotonic saline, or twice isotonic saline ( $C_s = 0, 165$ , and 330 mN respectively); we have therefore listed the latter values and the corresponding  $C_i$ -values in the legend of Fig. 2.

For the four illustrative curves, which include the entire range of  $C_s$ - and  $C_i$ -values likely to be encountered,

ered in actual experiment,  $[E:C.]_{\epsilon,\pi}$  is minimal (0.9 to 1.3 m.eq. per liter) for  $f_1 = 1.00$ . Between the latter and an  $f_1$ -value of 0.5,  $[E:C.]_{\epsilon,\pi}$  increases slowly to a value of 1.8 to 4.0 m.eq. per liter. Thereafter it rises asymptotically so that at  $f_1 = 0.10$  its value is 9 m.eq. per liter for curve A and 91 m.eq. per liter for curve D. These values for the precision measure of  $C_s$  correspond to the standard deviation for a single determination. In actual practice each chloride (or acidity) and each phenol red determination is done in duplicate; hence, all of the foregoing  $[E:C.]_{\epsilon,\pi}$ -values may be divided by 1.4 (i.e.,  $\sqrt{2}$ ) in estimating the reliability of the final mean value for any  $C_s$ .

It is apparent from the foregoing that, on occasion, values for  $[E:C.]_{\epsilon,\pi}$  may be so large that they deprive the final value for  $C_s$  of all its quantitative significance. This may arise when the experimental conditions are such as to lead to values for  $C_s$ ,  $C_i$  and  $f$ , which correspond to the higher portions of the curves in Fig. 2. Although in our work with the dilution indicator technique such combinations of these three factors have occurred infrequently, other applications of the method may lead to these conditions more often. It is with this possibility in mind that the foregoing discussion of the precision of  $C_s$  has been presented in such a manner as to include situations which are not usually encountered in fractional gastric analyses.

#### EXPERIMENTAL PROCEDURES FOR INCREASING THE RELIABILITY OF THE DILUTION INDICATOR TECHNIQUE

To maintain the dilution indicator method at a maximum of reliability its several precision measures must be reduced to the lowest values attainable experimentally. From equations (4) through (6) it is apparent that such reduction can be effected only by modifications in procedure which will increase the values for the constants in the denominators of these equations and decrease those in the numerators. Thus:

(a) The proportion of secretion in each gastric sample ( $f_1$ ) must be kept as large as possible. Under certain conditions a  $C_s$ -value may be completely invalidated by an  $f_1$ -value less than, say, 0.1. In order to maintain  $f_1$  at a high value, the initial volume of test-meal must be kept as low as possible and the rate of secretion as high. These conditions may be effected by the use of a modification of the "block method" of gastric analysis as described by Wilhelmj, Neigus and Hill (1933). According to this method a small volume of fresh test-meal is introduced into the stomach at the beginning of each quarter-hour period, and is removed completely at the end of the period—together with the accumulated secretion. However, such adjustment of the experimental conditions may not always be feasible in the light of the purposes of the experiment; when this is the case,  $C_s$ -values corresponding to low  $f_1$ -values must be viewed with the gravest suspicion.

(b) The precision measures  $\epsilon$  and  $\pi$  must be kept as low as possible. The values employed in the foregoing calculations were established for the particular methods described, and it is conceivable that some other substance for the dilution indicator instead of phenol red might lend itself to a determination of higher reliability. We have not as yet been able to discover a suitable substance of this kind, but we are considering the possibility of reducing  $\pi$  by the use of a photo-electric colorimeter in the phenol red determi-

nation. Also,  $\epsilon$  for the acidity determinations may be decreased appreciably by the use of an electrometric titration technique instead of the colorimetric, and we are at present investigating the applicability of a glass electrode set-up for this purpose. Electrometric titration for chlorides may similarly improve the accuracy of this determination, but as yet we have not studied this possibility.

(c) The concentration of phenol red in the test-meal ( $P_s$ ) occurs in the denominator of all the error equations except (6a); it might be concluded therefore that the corresponding  $[E:]$ -values will all be lowered by increasing  $P_s$ . This conclusion, however, is based on the assumption that  $\pi$  will not vary with  $P_s$ . Since  $\pi$  was determined for a single  $P_s$ -value, its magnitude for any other  $P_s$ -value can only be established experimentally. Hence the effect of a change in  $P_s$  on the errors caused by  $\pi$  cannot be predicted solely from the general equation.

(d) Since  $(C_o - C_i)$  occurs in the numerator of equation (6), any reduction in this difference will result in a diminution of the corresponding  $[E:]$ -value. Generally,  $C_i$  is determined by the requirements of the experiment and  $C_o$  varies throughout the course of the gastric analysis; under these conditions there is but slight possibility of using this method of decreasing the errors. However, in a series of experiments to be reported shortly,  $C_i$  varied relatively little and was approximately equal to  $C_o$ . In this situation the  $C_o$ -values also varied but slightly and were close to the values for  $C_i$ —a consequence of the generalization that the mixture of two solutions of approximately equal concentrations yields a solution of a concentration not greatly different from that of either constituent. Thus the magnitude of  $(C_o - C_i)$ —and therefore of the error in  $C_s$ —was reduced well below that for the experiments in which  $C_o$  and  $C_i$  differed considerably.

(e) All the  $[E:]$ -values are implicitly expressed as standard deviations for a single determination ( $\sigma$ ). In the course of a determination of  $C_s$ , however, it is our practice to determine each  $C_s$ - and  $P_s$ -value in duplicate. Hence, each final  $C_s$ -value is an average based on two determinations of phenol red and of chloride (or acidity), and the precision measure of such an average would be given by the standard deviation of the mean ( $\sigma_m$ )—which is  $1/1.4$  (or  $1/\sqrt{2}$ ) times  $\sigma$ . Thus, the consistent practice of performing all analyses in duplicate will also exert some effect on reducing the  $[E:]$ -values of the dilution indicator technique.

#### SUMMARY

The dilution indicator technique in gastric analysis is a test-meal procedure for studying the composition of the secretion and its rate of formation in unoperated stomachs. Its use in gastric pouch experiments for studying secretory, absorption, and ionic interchange phenomena is also suggested. By correcting the observed concentration values (chloride, acidity, etc.) for test-meal dilution of the secretion, the volume and composition of the latter can be calculated. This correction depends on the presence in the test-meal of a substance (the dilution indicator) which is (1) non-toxic, (2) not absorbed in the stomach, (3) not destroyed, precipitated, nor absorbed, by any constituent of the stomach contents, (4) unable to interfere with acidity or other determinations, and (5) capable of analytical determination by a relatively simple pro-



cedure with a precision of at least 1 per cent. Phenol red (phenolsulfonphthalein) is shown to be the only substance which is known to satisfy all of these requirements.

Following a demonstration of the suitability of phenol red for the purposes of the dilution indicator technique, derivations are presented for the formulae employed in such gastric analyses, i.e., for the proportions of secretion and test-meal in any gastric sample, and for the corrected concentration of chloride or acidity. The present report then proceeds to investigate a hitherto unsuspected error in this method which may become extremely large under some circumstances. From its inception in 1896, the history of the dilution indicator technique reveals a succession of such errors which had to be eliminated one by one. The source of error treated in this contribution results from the compounding of analytical errors by reason of the calculations inherent in this type of gastric analysis. Hence, it is of such a nature that it can be made apparent most easily by a mathematical analysis of the entire situation.

It is generally recognized that when the several gastric fractions are analyzed for acidity, chloride, and phenol red concentrations, the resultant values always involve experimental errors of greater or less degree. These errors are usually expressed statistically, in terms of the standard error (or the probable error) of a series of determinations on solutions of known concentration. By means of the standard errors of the several analytical procedures and the formulae employed in the dilution indicator method, we have worked out the mathematical equations for calculating the precision measures (expressed as standard errors) of the final corrected chloride concentration or acidity as well as for the proportions of solution and test-meal present in each sample. Actual values for these errors have been calculated for a variety of conditions and the corresponding graphs plotted. From a study of these graphs it has been shown that under specified conditions the uncertainty in the corrected concentration values can be so great as to deprive the results of all quantitative significance. By way of illustration let us suppose a gastric analysis is done with a salt-free test-meal and that one of the gastric specimens is found to consist of nine-tenths original test-meal and one-tenth secretion. Then, in the first place, the fraction 1/10 will have a standard error of about 3 per cent. Furthermore, the standard error of the corrected chloride concentration in this specimen will be around 10 milli-equivalents per liter if the observed chloride concentration is very low, but it will increase rapidly with a rise in the latter, e.g., 25 and 50 milli-equivalents per liter for observed concentrations of 50 and 105 mM respectively. If one recalls that a standard error of 10 milli-equivalents per liter corresponds to a possible range of error of about 3 times this value, or 30 milli-equivalents per liter, it becomes apparent that the errors of the dilution indicator technique may sometimes become excessive for the purposes of physiological investigation. Several modifications in procedure, designed to reduce the size of these errors, are discussed and we are now investigating the efficacy in this respect of a photo-electric colorimeter (instead

of a visual instrument) for the phenol red determinations.

In addition to the foregoing source of error in the dilution indicator technique, another one—arising from fluid absorption in the stomach—was recently described in a study of corrected gastric analysis curves in man (Penner, Hollander and Post, 1940). The phenomenon has been studied in detail with dogs and a report of this investigation is now being prepared for publication.

#### ADDENDUM I

Equations (1)-(3a) may be derived as follows: since the gastric sample is a mixture of test-meal and secretion,  $f_t + f_s = 1$  and we may write

$$(P_t f_t) + (P_s f_s) = (P_o) \quad (1a)$$

$$\text{and } (C_t f_t) + (C_s f_s) = (C_o) \quad (1b)$$

where  $P_t$  is the concentration of phenol red in the secretion, which equals  $O$ . It follows therefrom that

$$f_t = \frac{P_o}{P_t} \quad (1)$$

$$\text{and therefore } f_s = \frac{P_t - P_o}{P_t} \quad (2)$$

Also, by substitution of (1) in (1b), we get

$$C_o = \frac{C_o - C_t f_t}{f_s} = C_t + \frac{C_o - C_t}{f_s} \quad (3)$$

and if  $C_s = O$ , then

$$C_t = \frac{C_o}{f_t} \quad (3a)$$

#### ADDENDUM II

The error equations (4)-(6) have been derived as follows: By definition, we have

$$[E:f_t]\pi = df_t \quad \text{and} \quad [E:f_s]\pi = df_s$$

Hence, by differentiating (1) and (2) respectively, and substituting  $\pi = dP_o$ , we obtain

$$[E:f_t]\pi = \frac{dP_o}{P_t} = \frac{\pi}{P_t} \quad (4)$$

$$\text{and } [E:f_s]\pi = \frac{dP_o}{P_t} = \frac{\pi}{P_t} \quad (\text{in absolute units}) \quad (5)$$

In order to develop  $[E:C_t]_\epsilon$  and  $[E:C_t]\pi$  let us first expand  $C_t$  by Taylor's theorem: Given  $C_t = f(C_o, P_o)$  and  $\epsilon = \Delta C_o$  and  $\pi = \Delta P_o$ .

Then, by Taylor's theorem

$$f([C_o + \Delta C_o], P_o) = f(C_o, P_o) + (\Delta C_o) \left( \frac{\partial f(C_o, P_o)}{\partial C_o} \right)$$

where terms of the second and higher orders may be neglected.

$$\text{But } [E:C_t]_\epsilon = f([C_o + \Delta C_o], P_o) - f(C_o, P_o)$$

$$\text{Therefore } [E:C_t]_\epsilon = (\Delta C_o) \left( \frac{\partial f(C_o, P_o)}{\partial C_o} \right) = (\epsilon) \frac{\partial C_t}{\partial C_o}$$

$$\text{Similarly } [E:C_t]\pi = (\pi) \frac{\partial C_t}{\partial P_o}$$

Evaluating these partial derivatives from equation (3), we obtain:

$$[E:C.]_{\epsilon} = (\epsilon) \left( \frac{P_i}{P_i - P_o} \right) = \frac{\epsilon}{f_i} \quad (6a)$$

$$[E:C.]_{\pi} = \left( \frac{\pi}{P_i} \right) \left( \frac{C_o - C_i}{f_i^2} \right) \quad (6b)$$

which represent the (partial) errors in the *corrected concentration* value ( $C_i$ ) caused by the errors in determination of chloride (or acid) and phenol red concentration respectively. If these partial errors are given as standard deviations, the total error in  $C_i$  is equal to the square root of the sum of the squares of the partial errors, i.e.,

$$[E:C.]_{\epsilon, \pi} = \sqrt{([E:C.]_{\epsilon})^2 + ([E:C.]_{\pi})^2}$$

By substituting (6a) and (6b) in this relation we obtain

$$[E:C.]_{\epsilon, \pi} = \frac{1}{f_i} \sqrt{\epsilon^2 + \pi^2 \left( \frac{C_o - C_i}{P_i f_i} \right)^2} \quad (6)$$

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## Editorial

### GASTROSCOPY IN DOGS

EVER since Helsley in 1923 trained his dog so that it allowed him to introduce a rigid gastroscope without anaesthesia, the dog has frequently been used as a subject for the practice of gastroscopy. However, the recommendations made in 1937 (Schindler: *Gastroscopy*, Chicago, 1937, pages 84-5) seem to have been disregarded, and on the other hand, new experiences have been gained so that it seems to be worth while to discuss this subject briefly, especially because physiologists will now frequently use gastroscopy in the dog as a method of physiological research.

Gastroscopy in the dog is extremely easy because the esophagus of the dog is very large and the introduction of an instrument is without difficulty. The use of an old rigid gastroscope is preferable to the use of a flexible gastroscope. Examination of the dog lying on its side is inadvisable since in this position too many shadows will disturb the visualization. The dorsal recumbent position is the best one. The dog should be anesthetized. A good anesthesia is obtained with intravenous injection of a 5 per cent solution of nembutal. We have tried to anesthetize the dog's throat with a 10 per cent solution of cocaine, but the effect has not been satisfactory. The dog should not receive food or water for twelve hours before the examination. The use of a muzzle during this period of time should be considered because without such a precaution the dog might swallow its own hairs, and that will alter the picture of the gastric mucosa. The nembutal solution should be injected slowly. The mouth is held open by a gag. The left index finger of the examiner is introduced into the mouth and should palpate the epiglottis. The epiglottis is lifted somewhat; the right hand grasps the instrument like a pencil, introducing it exactly in the middle line, exerting a rather sharp pressure toward the spine and pushing it easily into the stomach, which can be missed only if there is a deviation from the middle line. In unusually large dogs the length of the instrument, always adequate for the examination of men, may not suffice to see all of the stomach.

Formerly it was stated that the pylorus of the dog usually could not be seen at all; but in the meantime Dr. Alfred J. Klein and I have found a trick which enables the visualization of the pylorus in practically every case. In the dorsal position the angulus will be found in the 2 or 3 o'clock position of the gastroscope. If then the position of the dog is changed so that its head is hyperextended, hanging down over the edge of the operating table always supported by the hand of an assistant) the tip of the instrument will be removed from the posterior wall, as a result of a lever movement, and then suddenly the whole of the antrum, and at its end the pylorus, will appear in the visual field. At first Dr. Klein and I used gastric fistulas in order to observe gastroscopically the gastric antrum of the dog; but since the discovery described, we were able to give up these unsatisfactory operative procedures. Gastroscopy through a gastric cannula has the one advantage that it may enable us to see the rosette-like cardia.

The mucosa of the dog's stomach looks entirely different from the human gastric mucosa. All observers have agreed to call the color of the human gastric mucosa orange-red. In checking Dr. Klein's case protocols, I have found that in none of 18 dogs was the color of the gastric mucosa called orange-red. In 5 dogs there was a definite difference in the color of the lower one-third and the upper two-thirds of the stomach, a feature not occurring in human stomachs. In all these 5 cases the lower portion looked darker than the upper portions, irrespective of air inflation. The color of the lower portions was called either pinkish-red, or reddish, or pink. That of the upper portions was called either pink-gray or gray, or light pink. In 10 cases the color of the stomach was uniformly denoted either as pinkish, or dark pink, or pinkish gray, or red. In the remainder no notation was found in the protocol concerning the color. As described in my book, in frequent cases blue blood vessels were observed, especially in the upper portions of the anterior wall and of the greater curvature even when the stomach was not distended in an unusual

way. Then a picture was obtained which resembled slightly the well-known picture of severe atrophic gastritis in human beings. It should be stated that in healthy men this picture can not be obtained regardless of the amount of air introduced into the stomach.

The posterior wall of the stomach protrudes into the

cavity, but with the trick mentioned above usually becomes visible, if a rigid gastroscope is used. The lesser curvature is short. The peristalsis of the antrum does not show the regular waves observed in man. The pylorus closes in a rather irregular form, with a kind of star-like formation.

Rudolf Schindler.

## Abstracts of Current Literature

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RAPOPORT, S. AND GUEST, GEORGE MARTIN: *The Role of Diphosphoglyceric Acid in the Electrolyte Equilibrium of Blood Cells: Studies of Pyloric Obstruction in Dogs.* *J. Biol. Chem.*, 131(2):675-689, 1939.

After pyloric obstruction, an increased conc. of diphosphoglycerate in the blood cells was found to be the most important factor compensating for the decreased conc. of Cl. The measurements included detns. of total base, Cl, CO<sub>2</sub>, pH, sp.gr., water content, inorganic P, organic acid-soluble P, and diphosphoglycerate. Values for total base agreed closely with the sums of the anions in the cells of all blood samples. Distr. ratios of the diffusible ions H, Cl<sup>-</sup>, and HCO<sub>3</sub><sup>-</sup> in serum and cells agreed closely with the ratios calculated from the non-diffusible anions by means of the formulae of Van Slyke, Wu and McLeon. The distr. of the diffusible ions was found to depend mainly upon the conc. and anion equivalency of Hb and diphosphoglycerate.—Authors (Courtesy of Biol. Abst.).

BUSSABARGER, R. A., IVY, A. C., WIGODSKY, H. S. AND GUNN, F. D.: *The Effect of Gastrectomy on the Monkey.* *Ann. Internal Med.*, 13(6):1028-1041, 1939.

Hematologic studies on 5 gastrectomized monkeys in the 2.66 year period following gastrectomy failed to reveal any evidence of pernicious anemia. The additional stress of a Wills diet (low in Castle's extrinsic factor) fed to 3 gastrectomized and 2 normal monkeys also failed to produce pernicious anemia. Pregnancy in one of the gastrectomized monkeys failed to produce an anemia, but a hypochromic anemia developed during the puerperium.—H. S. Wigodsky (Courtesy of Biol. Abst.).

GESSLER, C. J., DEXTER, S. O., ADAMS, MARGARET A. AND TAYLOR, F. H. L.: *Observations on the Etiologic Relationship of Achylia Gastrica to Pernicious Anemia. VIII. Further Studies of the Proteolytic Activity of Normal Human Gastric Juice in Vitro; and the Limitations of the Method in Pernicious Anemia.* *J. Clin. Invest.*, 19(1):225-231, 1940.

The so-called intrinsic factor in gastric juice which leads to remission in pernicious anemia was correlated with the proteolytic enzyme of the gastric juice in 2 additional respects. Adsorption by Lloyd's reagent completely removed both the clinical activity and the proteolytic power of gastric juice. Dialysis of gastric juice for periods of 3 to 5 days did not impair either the activity of the gastric juice in patients with pernicious anemia or the proteolytic activity of this material against casein. The use of the proteolytic activity of gastric juice as a means of diagnosing pernicious anemia was found unsatisfactory because of the presence of large amounts of tryptic-like

enzymes in the gastric juice of patients with pernicious anemia.—F. H. L. Taylor (Courtesy of Biol. Abst.).

HAWKSLEY, J. C.: *A Note on the Occurrence of Pieces of Sloughed Gastric Mucous Membrane in Aspirated Gastric Juice.* *J. Path. and Bact.*, 49(3):485-487, 1 pl., 1939.

The histological appearance of gastritis are described in pieces of sloughed mucous membrane aspirated in the resting juice prior to gastroscopy in 200 cases. These sloughs are believed to have separated naturally and prior to aspiration.—J. C. Hawksley (Courtesy of Biol. Abst.).

NECHELES, H., HANKE, MARTIN E. AND FANTL, ERICH: *Preparation and Assay of Inhibitor of Gastric Secretion and Motility from Normal Human Urine.* *Proc. Soc. Exp. Biol. and Med.*, 42(2):618-619, 1939.

Normal human urine was subjected to fractional precipitation with (NH<sub>4</sub>), SO<sub>4</sub> and alcohol, and a white water soluble non-toxic powder was obtained with depressed and abolished gastric secretion and motility of dogs in amounts of 1 to 4 mgs. Dogs with Pavlov pouches and gastrotomies respectively were employed. A standard meat meal was used in tests for secretion, and insulin in tests for motility. Preps. which had not been highly purified, contracted the dog's gall bladder and increased secretion of bile.—Authors (Courtesy of Biol. Abst.).

SIMICI, D., DIMITRIU, C. C. ET TANASOKA, T. *Recherches Gastrographiques Concernant l'action des Solutions Hypertoniques de Chlorure de Sodium sur la Motilité et Tonicité de l'estomac.* *Bull. Acad. Med. Roumanie*, 7(2):77-85, 5 figs., 1939.

Intravenous injection of the hypertonic solution in dogs showing, at the time of injection, normal or weak gastric contractions leads to complete inhibition of motility and tonicity. The same treatment in an animal in which hypertonicity is mechanically produced is followed by further augmentation of the tonicity.—F. H. Snyder (Courtesy of Biol. Abst.).

MONASTERIO, GABRIELE: *La Sindrome Anemica del Carcinoma Gastrico e sua Patogenesi.* *Haematologica Arch.*, 20(5):443-503, 9 figs., 1939.

Hemopoiesis was studied in 33 cases of gastric carcinoma. The anemia present is usually hypochromic, rarely normochromic and exceptionally hyperchromic, without hemolytic complications. The mean corpuscular diameter was usually normal, rarely diminished, but never increased. The number of white blood cells was usually normal with the neutrophilic polymorphonuclears slightly

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increased and, at times, there was histiocytosis present. The sternal bone marrow showed, in the majority of cases, a normal erythropoiesis, or a hyperactivity, as judged by the presence of myeloblasts and normoblasts and basophilic granulation. At times there was insufficiency despite the presence of normal, or even increased hemopoiesis. The plasmocytes were, at times, increased, exhibiting histiocytic characteristics. The Singer test (increased reticulocytes, 4 to 5 days following injection of 3 cc. of gastric juice) performed in a few cases, was positive where the bone marrow was megaloblastic. The pathogenesis of the anemia in gastric carcinoma involves 3 fundamental factors: (1) achylia and the digestive disturbances resulting from it; (2) toxic influences on the bone marrow by the toxins of the cancer cells; (3) the continuous loss of blood. Consequently, the hemopoietic alterations may present all the characteristics of the anemias of non-neoplastic achylia, the neoplastic anemias, pernicious anemia and the anemia of hemorrhage, with prevalence of one or the other, corresponding to the greater intensity or duration of the different pathogenic factors.—S. Nittis (Courtesy of Biol. Abst.).

TUDORANU, G., DIMITRIU, C. C. ET TANASOCA, T.: *L'action des Solutions Hypertoniques de Glucose sur la Motilité et la Tonicité de l'estomac chez l'homme*. Bull. Acad. Med. Roumanie, 8(4):312-314, 5 figs., 1939.

Intraven. inj. of 33% glucose solution in doses of 100 cc. decreases the motility and tonicity of the stomach. Smaller doses (6.6 to 15.5 g. of glucose) have no effect.—F. H. Snyder (Courtesy of Biol. Abst.).

TUDORANU, G., DIMITRIU, C. C., WASSERMAN, L. ET NEGRUTZI, R.: *Contributions a l'étude de l'absorption Rectale sur le Chimisme Stomacal Chez l'homme*. Bull. Acad. Med. Roumanie, 7(2):112-123, 6 figs., 1939.

Rectally administered NaCl, MgSO<sub>4</sub>, and bouillon stimulate the secretion of acid by the stomach; glucose depresses gastric secretion; olive oil (which is not absorbed by the rectal mucosa) and NaHCO<sub>3</sub> have no effect.—F. H. Snyder (Courtesy of Biol. Abst.).

BLOOMFIELD, ARTHUR L.: *The Decrease of Gastric Secretion with Advancing Years: Further Observations*. J. Clin. Invest., 19(1):61-63, 1940.

Histamine tests repeated in the same individuals after periods of 10 or more years show little or no change in some subjects, whereas in others there is a marked fall in gastric secretion. The average curve of decline of gastric secretion with advancing years is a resultant of various findings of this sort. Basal gastric secretion also declines with advancing years.—A. L. Bloomfield (Courtesy of Biol. Abst.).

GAMMEI, G. AND BAYER, H.: *Roentgensymptomatologie der Divertikelmyme des Magens*. Fortschr. a. d. Geb. Roentgenstrahlen, 61:3-163, March, 1940.

The authors describe a rare case of a myoma of the lesser curvature of the stomach. The roentgenological picture was similar to that of a perforation of a gastric ulcer however the form and shape of the fistula had a different appearance at three examinations. The lesser curvature near the base of the fistula was irregular so that the pre-operative diagnosis was that of an ulcerated malign tumor. Even the autoscopic control was unable to explain the roentgenological findings as no fistula could be seen! Even the microscopic diagnosis varied between that of a benign neurinoma and myoma.—Franz Lust.

MOUTIER F. AND GHELEW, B.: *Etude Endoscopique de L'Estomac Opéré; Evolution Post-Opératoire des Lésions et Lésions Post-Opératoires*. (Gastroscopic Studies on the Operated Stomach and Postoperative Pathology). Arch. des Maladies de L'Appareil Digestif et des Maladies de la Nutrit., Vol. 29, No. 8, p. 817-833, 1939.

Gastroscopy was done on 145 patients on whom previous

operations for ulcer had been performed: 96 gastro-enterostomies; 33 subtotal gastrectomies; 2 plastic operations; and 14 repairs for perforations. The 14 perforated ulcers had been submitted to the following operations: primary repair, 6; repair following gastro-enterostomy, 6; subtotal resections, 2. The 33 resections were done by various methods: Péan-Billroth I; Billroth II; Polya; Finsterer; Polya and Finsterer; wedge resection; Finney. *Gastroscopic observations following gastro-enterostomy:* Contraction of the walls of the stomach, spasm and generalized edema were seen frequently. The gastro-enterostomy stoma opened and closed rhythmically in a few cases with no synchronism with pyloric activity. *Ulcers following gastro-enterostomy or subtotal resection:* out of a total of 96 gastro-enterostomies and 33 resections, 22.9% and 27.2% respectively returned with ulcers, and 49% and 46.5% respectively returned with gastritis. The reasons why patients with gastro-enterostomies returned to the hospital were the following: ulcer pain 38.5%; gastritis symptoms 36.6%; stenosis, etc. 9.3%; hemorrhage 9.3%; and 4% loss of weight, anemia, nervousness, etc. Following subtotal gastrectomy patients returned to the hospital for the following reasons: ulcer pain 36.4%; gastritis symptoms 37.4%; hemorrhage 12.1%, and anemia 3.3%. Following gastro-enterostomy it is not rare to see an old ulcer become active again. Sometimes a gastric ulcer will heal but a duodenal ulcer will continue to remain active. In one case a duodenal ulcer began to show active symptoms 13 years following gastro-enterostomy. Another patient had a hemorrhagic gastritis after 15 years of perfect results following gastro-enterostomy. Others had ulcerative gastritis, jejunitis with marginal erosions, or ulcers immediately following gastro-enterostomy. Of 96 gastro-enterostomies the authors have observed 14 new ulcers (14.6%); 8 marginal and 6 fundic. In 33 subtotal resections the authors found 9 new ulcers (27.2%) of which 5 were marginal and 4 in the fundus. Of the total number of operated cases, 8 had marginal ulcer following gastro-enterostomy and 5 following total resection. That is 8.3% of the gastro-enterostomies and 15.2% of the subtotal resections. The authors underline that, contrary to most other investigators, they found nearly twice as many marginal ulcers following subtotal gastrectomy than after gastro-enterostomy.

A marginal ulcer may escape diagnosis by X-ray and is seen frequently only with the gastroscope. The authors quote a case on whom a Finsterer resection was performed; the patient, 30 years of age, experienced epigastric pain a few days after operation. The gastroscope revealed a large gastrojejunal ulcer, and a second resection was performed. Four months later the patient became ill again and an erosion was seen at the stoma.

The authors underline that gastritis frequently is accompanied by the typical syndrome of ulcer. It is impossible therefore, they say, to decide without gastroscopy whether symptoms are due to gastritis or ulcer.

Gastrojejunitis is usually accompanied by a considerable hypersecretion of mucus. The mucosa may be very fragile, and hemorrhage easily. Blood spots and purpura (Schindler) are seen frequently.

In no case hyperchromic anemia was seen, but very frequently secondary anemia, not due to hemorrhage. A few cases are described in whom hemorrhage occurred, although neither X-ray nor gastroscopy could establish a bleeding ulcer. Punctiform hemorrhage was observed in some of these cases, in one of whom a new resection had to be performed in order to save the patient.

Concerning which type of operation to use, the authors believe that every case has to be judged by itself. They are in favor of extensive resections, if necessary, in order to protect the patient against recurrence, but even at that they have seen such cases return with ulcers in the stump of an extensively resected stomach. They believe that subtotal gastrectomy avoids the formation of ulcers by taking out a large part of the area in which they usually occur,

but that this operation is no guarantee against recurrence of "Ulcer disease."—H. Necheles.

TRAVELL, JANET: *The Influence of the Hydrogen Ion Concentration on the Absorption of Alkaloids from the Stomach. J. Pharm. and Exp. Ther.*, 69:21, 1940.

Experiments carried out in the cat and dog using several alkaloids (strychnine, nicotine, cocaine, atropine and physostigmine) show that in the animal with ligated cardia and pylorus, alkaloids are not absorbed to any extent from the stomach when the reaction of the gastric juice is strongly acid. If the gastric juice is rendered alkaline, however, alkaloids are rapidly absorbed from the ligated stomach. Under these conditions, strychnine is absorbed practically as well from the gastric mucosa as from the subcutaneous tissues. In the normal animal, the administration of sodium bicarbonate in an amount sufficient to neutralize gastric acidity increases the toxicity of strychnine given orally, reducing the minimum fatal dose by about one-third. In the normal animal, the administration of hydrochloric acid does not increase the oral minimum fatal dose of strychnine, but materially delays the onset of tetanus. This delay is probably due to the time required for neutralization of acid in the small intestine, for a similar delay is observed when strychnine in acid solution is injected directly into a ligated intestinal loop.—A. E. Meyer.

SANDRONI, DINO AND SAGAL, ZACHARY: *The Popularity of the Ewald-Boas Test Meal: Reasons for Its Survival. Ann. Int. Med.*, XIII, 2134, May, 1940.

The authors' evident purpose is to justify a carbohydrate test meal and single removals. No contrast studies were done and none of their cases showed an abnormality of the blood. Though the material studied was taken from a gastro-intestinal clinic, a surprisingly small per cent showed an achlorhydria. Of 2153 patients on whom gastric analyses were done only 11.3 per cent showed no free HCl on single specimen study, and this was reduced to 7.5 per cent by repeating the studies with fractional removal method. These are classified as achlorhydrias but only free HCl is mentioned in the text. No recognition is given to combined HCl. This 7.5 per cent of so-called achlorhydrias is yet further reduced to 5.6 per cent by the use of histamine. Of the cases showing no free HCl on single aspiration about 50 per cent showed HCl on fractional removals.

The authors conclude that (a) single removal and a carbohydrate meal are satisfactory and yield adequate information in 90 per cent of cases. (b) The remaining 10 per cent may be subjected to more detailed study, such as fractional removal, histamine, neutral red and other methods. (c) That gastric analysis continues to be a worthwhile procedure.—Virgil E. Simpson.

DEBAKEY, MICHAEL AND ODOM, CHARLES B.: *Significant Factors in the Prognosis and Mortality of Perforated Peptic Ulcer. Southern Surgeon*, 9:425-437, June, 1940.

Acute perforation of gastro-duodenal ulceration is of serious moment since there is an apparent increase in its incidence and no appreciable decrease in the mortality which continues at about 25 per cent. Certain factors seem to play an important part in the prognosis and mortality of perforation. The condition is more likely to be fatal in males and there is a definite increase in mortality directly in relation to advancing age. Perforation is more fatal in gastric than in duodenal ulcers probably because in the former the average age is greater and the spillage of contents larger. The time elapsing between perforation and operation is one of the most significant factors. Six hour periods afford probably the best units for consideration and the increasing mortality in each successive period is most alarming. While occasionally low mortality due to walling off or plugging off the perforation may be shown in cases where operation is delayed, this occurrence cannot

be depended upon. Spinal anesthesia appears to be definitely safer than does general which gives less relaxation and increased toxicity. Local anesthesia shows the highest mortality probably because it is usually used on the poorest risks. Statistics based upon the type of operative procedure must be evaluated by a consideration of the selection of cases and familiarity with various types of operation. Since the method of choice should be the one which effects most expediently adequate repair of the defect the authors prefer simple closure with reinforcement by omental graft where convenient. Wound infections (including evisceration) represent the highest incidence of complications and hemorrhage the most fatal of complications when it occurs but most deaths are due to peritonitis or pulmonary affections.

A large number of references are listed at the close of the article.—J. Duffy Hancock.

WILLCOX, PHILIP H.: *Gastric Disorders in the Services. British Med. J.*, 2:1008, No. 4146, June 22, 1940.

Studies of medically unfit soldiers indicate a very high incidence of stomach and duodenum disorders. Examination of 260 cases returned from France showed that 65 or 25 per cent were attributed to disorders of the stomach and duodenum. This did not include reflex dyspepsia secondary to appendicitis and cholecystitis. The group of disorders which include gastric and duodenal ulcers (approximately 50 per cent), chronic gastritis and functional dyspepsias, outclasses in incidence any other group. A study of 238 cases returned from France, 174 were medical, of which no fewer than 41 or 23.5 per cent were cases of gastro-duodenal disorders. The author comments on the number of cases with pyloric spasm without evidence of ulceration, in which he had found chronic gastritis in a number of these cases. He has found that army life causes an aggravation of the diseases in patients who had previously suffered from them, but there is no evidence as yet to show that the diseases will originate in soldiers who are healthy.—Maurice Feldman.

SLAVE, ALEXANDER, BACHRACH, WILLIAM H. AND FOGELSON, SAMUEL J.: *The Significance of Nutrition and Gastric Acidity in the Etiology of Experimental Peptic Ulcer. S. G. O.*, 70:3-666, March, 1940.

This study describes the Mann-Williamson method for experimental production of peptic ulcer in dogs and the consequent state of declining nutrition. Twenty-eight dogs were used and control values were established by means of fractional gastric analyses. The operation was divided into three stages. In the first stage, the distal end of the duodenum was anastomized to the small intestine at a point 120 centimeters distal to the gastrojejunal anastomosis. This resulted in increased acidity of the gastric juice but was not due to alteration in the ability of the gastric glands to secrete acid juice.

The animals were studied for 13 weeks and after ruling out jejunal ulcer, the second stage operation was performed. A segment of the intestine between the duodeno-ileostomy and cecum was resected so only 40 centimeters of ileum remained between the two points. Though this did not alter the gastric acidity factor, the nutritional factor was reduced. The third stage was converted into the first stage by restoring the Thiry loop used in the second stage to normal. However, this did not prolong the dogs' lives.

As a result of these experiments, it was observed that the incidence of jejunal ulcer subsequent to drainage of the duodenum into the small intestine is decreased if the point of drainage is close to the site of gastrojejunal anastomosis. After operation, gastric acidity response to an alcohol meal and histamine was higher than before though there is no relation between this and the incidence of jejunal ulcer.

Dogs which maintained nutrition and even gained weight after the high duodenal drainage operation developed

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ulcers when nutrition was impaired by a resection of considerable small intestine between the point of drainage and the cecum.—Francis D. Murphy.

DRAKE, MILES E., MODERN, FRED S., RENSHAW, R. JOHN F. AND THIENES, C. H.: *A Pharmacological Approach to the Effector Innervation of the Small Intestine*. *Arch. Internat. Pharmacodyn. et Ther.*, 63(2):224-242, 5 figs., 1939.

Rabbit and rat vagi were cut between stomach and diaphragm; rabbit splanchnics were cut just below the diaphragm; in some, vagi and splanchnics were both cut; one or several branches of mesenteric nerves of rabbits, cats, monkeys and guinea pigs were cut; and 3 days to 3 months were allowed for nerve degeneration. None of the operations altered responses of excised gut to acetylcholine, pilocarpine, eserine, nicotine, BaCl<sub>2</sub> or KCl. Splanchnic degeneration slightly sensitized to epinephrine, but did not alter response of gut wall or blood vessels to electric stimulation of mesenteric nerves. Mesenteric nerve degeneration sensitized smooth muscle and vessels to epinephrine. Vagus fibers are preganglionic and end in myenteric ganglia. Sympathetic fibers of splanchnics are preganglionic also, but sympathetic fibers of mesenteric nerves are postganglionic.—G. A. E. (Courtesy of Biol. Abst.).

KLASON, T.: *On Perforated Gastro-duodenal Ulcers and Their X-ray Diagnosis*. *Acta Med. Scand.*, 102(1/2):132-139, 2 figs., 1939.

The author describes 81 cases of operated perforated ulcers: 32 gastric and 49 duodenal ulcers. Mortality was 17.3%. In relation to the 24 hours the perforations were not evenly distributed, but showed 3 peaks: morning, afternoon and midnight. The perforations occurred in the majority of cases 2-3 hours after a meal. Trauma is, in normal conditions, only of slight importance in the origin of perforation. It was possible to demonstrate air in the peritoneum in 72 out of 81 cases (89%). Of 32 patients with gastric ulcers, peritoneal air was demonstrable in 29, and of 49 patients with duodenal ulcers, air was found in the peritoneum of 43.—J. F. Wilkinson (Courtesy of Biol. Abst.).

LAHEY, FRANK H.: *A New Plan of Antecolic Duodeno-jejunal Anastomosis*. *S. G. O.*, 70:3-689, March, 1940.

A very difficult problem at times is the restoration of the alimentary canal after resection of the jejunum at such a high level that there remained such a short intraperitoneal stump that lateral anastomosis is impossible and end-to-end is unsafe.

The new procedure described is one in which the upper jejunum is resected distal to the ligament of Treitz. The next step is mobilizing the colon after the parietal peritoneum has been cut to allow the duodenum and remaining jejunum to go anterior to the colon. Finally, a lateral anastomosis is performed antecolic. This operation has proved very satisfactory in patients with a gastrojejuno-colic fistula in whom it was necessary to resect stomach and jejunum.—Francis D. Murphy.

BRUNN, HAROLD AND LEVITIN, JOSEPH: *A Roentgenological Study of Intestinal Obstruction*. *S. G. O.*, 70:5-915, May, 1940.

The authors state that X-ray findings along with clinical symptoms are of value in giving a clue as to the type of obstruction and the underlying cause. Either gas or barium may be used as a contrast medium to outline the gastro-intestinal tract.

This article divides intestinal obstruction into two types: one which is due to a block of the free passage of gas and fluid into the bowel—the mechanical or dynamic obstruction, and the other, which is of neurogenic origin and due to a stimulation of the sympathetic nervous system, which is inhibitory to the bowel, or to peritonitis. This may be

called the paralytic or adynamic ileus caused by infection, trauma, shock, severe pain and psychic factors.

The X-ray findings in a mechanical obstruction are large loops of gas distended bowel, accentuated peristalsis, free movement of gas and fluid with fluid levels tending to lie on the same horizontal plane. The movement of the diaphragm is limited only by distention.

In adynamic obstruction, distention is segmental and loops of small and large bowel are scattered over the abdomen. There is free movement of gas and fluid with change in the patient's position and lack of activity of the bowel. Peristalsis is absent.

In local peritonitis, there may be an ileus consisting of single or multiple loops of bowel at the site of infection and obliteration of the peritoneal fat line. In generalized peritonitis, there is distention of the bowel, which may involve the large as well as small bowel, of an adynamic nature, with loops scattered over the abdomen. Peristalsis is absent; there is limitation of movement of the diaphragm on the affected side or both sides. The loops of the distended bowel are small, shallow and relatively fixed in position. This is seen on the X-ray film by multiple fluid levels scattered over the abdomen.

Films should be taken with the patient in a supine position, an upright position and with the patient lying horizontally on his side.—Francis D. Murphy.

ROBINSON, DANIEL R. AND WISE, WALTER D.: *Simple Non-specific Ulcer of the Jejunum-ileum*. *S. G. O.*, 70:6-1097, June, 1940.

A simple ulcer of the small intestine is classified as such when it is not due to any of the known etiologic agents as typhoid, dysentery, tuberculosis, syphilis, uremia, gastroenterostomy, trauma and tumors. Only 57 such ulcers have been reported in the literature, 44 occurring in the ileum and 13 in the jejunum. Two cases are reported in this study.

Clinically the diagnosis has never been made and the ulcer was discovered at operation or post-mortem. The reasons for operation are usually some complication or obstruction, hemorrhage or perforation. These non-specific ulcers resemble peptic ulcers in that they have the same complications and histologically show only acute and chronic inflammatory changes.

Various theories as to the cause of these ulcers have been presented: focal infection, vascular obstruction, trauma, and lastly, some feel that there is a relation between this condition and the presence of heterotopic gastric mucosa in the small intestine. When these ulcers are brought to the attention of the physician, the treatment is surgical. Thirty-nine of the 57 patients were operated on; in 18 cases resection and anastomosis were done with 22 per cent mortality; 15 had simple transverse closure with 40 per cent mortality, and in 2 patients, the ulcer was excised and a transverse closure carried out with 50 per cent mortality.

From this small series it would seem that where possible, the procedure of simple closure with short-circuiting anastomosis to obviate possible stricture of the intestines is the safest choice.—Francis D. Murphy.

CHROM, SVEND A.: *On Comparison Between the Roentgenological and the Operative Findings in Acute, Mechanical Ileus*. *Acta Radiologica*, XXI, 2:182, April, 1940.

On the basis of a comparison of the roentgenological observation with the operative resp. post mortem findings Chrom discusses the value of the assistance which the roentgenological diagnosis is capable of giving in cases of acute, mechanical ileus. The determination, from abdominal roentgenographs taken without the use of contrast substance, of whether the gaseous dilatation is in the small or large intestine is fairly reliable. In sixteen of Chrom's nineteen cases the operative findings agreed with the evidence found by roentgenological examination. Fluid levels were present in the great majority of his cases, especially

of those with ileus of the large intestine. Chrom, however, emphasizes that the cause for a mechanical ileus of the small intestine can not be found without the use of contrast substance. A barium enema has to be administered to make sure that the obstruction is not situated in the colon, and on the other hand, makes it possible to locate an obstruction in the colon. In many cases the nature of the obstruction in the colon can be determined.—Franz J. Lust.

OPPENHEIMER, A.: *The Ileocecal Region. Radiology*, 34:545, May, 1940.

The ileocecal region is as common a site of motor disorder, inflammation, and newgrowth as are other parts of the digestive tract where two sections of different width, structure, and function join at a sphincter or valve. The author believes that the results of postmortem studies and animal experiments cannot be applied to this problem of human physiology. Oppenheimer presented an analysis of his studies of the ileocecal region of 86 apparently healthy persons. These studies indicated that in the terminal ileum, cecum, and ascending colon, opaque food is moved on chiefly by "systolic" tonic contractions which are preceded by "diastolic" relaxations due to loss of tone. The tonic variations are fairly rapid in the terminal ileum, but very slow in the ascending colon. A "receptive relaxation" of the cecum begins as soon as opaque food reaches the ileal loops proximal to the terminal loop. The cecum is normally low in position when it begins to fill, and rises while the contents are moved on into the transverse colon. The ileocecal valve remains closed while peristalsis in the terminal ileum is wave-shaped and rhythmic; it becomes passable when the opaque medium is driven forward by tonic "stripping" contractions in the terminal ileum. The valve is normally competent for opaque food given by the mouth. The cecocolonic sphincter is relaxed while the ascending colon fills, but contracts slowly while mass peristalsis drives the contents into distal parts. This contraction causes physiologic stasis in the cecum. The vermiform appendix is filled by the peristalsis of the cecum, but is emptied by its own intrinsic tonic contractions.—Robert Turell.

FALLIS, LAWRENCE S. AND MCCLURE, ROY D.: *Acute Cholecystitis; a Review of 320 Cases. S. G. O., 70:6-1022, June, 1940.*

This study consists of 320 cases of acute cholecystitis which were healed by cholecystectomy. As a rule, the operation was done as soon as possible. Cases were selected on the basis of pathological report rather than surgical or clinical judgment. The pathological criterion for the diagnosis of acute cholecystitis was microscopic evidence of polymorphonuclear infiltration of the gall bladder wall.

Three hundred and twenty consecutive cases of acute cholecystitis were operated on with a mortality of 5.3 per cent. The age of the patient had a very definite bearing on the mortality; for the 108 patients under 40 years of age there was one death—a mortality of .9 per cent, while in the group of 48 patients over 60 years of age there were 5 deaths, a mortality rate of 10 per cent, and in the middle group of 165 patients, there were 11 deaths with a mortality of 6.7 per cent.

The group of patients whose maximum pre-operative temperature was above 102 degrees F. showed a mortality rate two and a half times the mean death rate. Pulmonary complications increased the operative risk three times and cardiac complications doubled the risk.

In order to determine the proper time for operation, the cases were divided into three groups depending on the duration of the symptoms prior to operation. Group I includes those operated on within 24 hours, and in this group there was a mortality of 8.3 per cent. Group II consists of the patients who had symptoms from 24 to 72 hours before operation, and in this group the mortality was 7.3

per cent. The lowest mortality of 3.4 per cent was found in the last group where a period of over 72 hours elapsed from the onset of symptoms to the operation.

A diagnosis of chronic cholecystitis with acute exacerbation was made in 43 per cent of the patients. A previous attack of cholecystitis or long-standing gall bladder disease appears to confer some degree of immunity, for the lowest operative death rate of 3.6 per cent was found in the group of patients whose acute cholecystitis was superimposed upon pre-existing cholelithic disease. Further evidence on this point is that the death rate following operation on the same number of patients with primary acute cholecystitis was 6.1 per cent. Gangrene of the gall bladder with surgical interference gave 10 per cent mortality, empyema 5.9 per cent. Gall stones were present in all but 9 per cent of the cases.

From this study, it would appear better to delay operation until the acuteness of the process has subsided and the patient has been given the proper pre-operative treatment.—Francis D. Murphy.

SCHALM, L.: *Le Diamètre Moyen des Globules Rouges Comme Élément de Diagnostic dans la Différenciation des Ictères. The Average Diameter of the Red Blood Cells as a Diagnostic Factor in the Differentiation of the Types of Icterus.*

It has been known for quite some time that the diameter of the red blood cells in liver cirrhosis and in some forms of icterus is increased. The study of the average diameter of the red blood cells permits the differentiation of icterus caused by alterations of the parenchyma of the liver and the icterus caused by obstruction of the biliary ducts. In a case of icterus, an increase of the average diameter of the red blood cells of 1.0 u, or more, indicates with great probability an extensive destruction or an important functional alteration of the liver tissue, which could be the cause of the icterus without obstruction of the biliary ducts. (Only one exception, in a case of carcinoma of the head of the pancreas, was noted). On the other hand, such an increase permits with great probability the exclusion of an obstruction of the biliary ducts by stones without serious damage of the liver tissue itself. If in a case of icterus lasting for several weeks the diameter does not exceed 0.7 u, then an obstruction without serious affection of the liver tissue can be assumed.—Rudolf Schindler.

BERG, HANS HEINRICH: *Gasfuehlung der Gallenwege. Weiteres ueber den Nachweis von Gas in den Gallenwegen. Fortschr. u. d. Gebiet d. Roentgenstrahlen, 61:1-1 and 8, Jan., 1940.*

Gas may be found in the hepatic ducts (1) by perforation of gas or air containing organs into the ducts or (2) by infection with gas producing bacteriae.

Berg emphasizes that the diagnosis can be made without the use of contrast media ("flat plate.") He describes several cases of cholecysto-duodenal fistulae in which air can be seen in the hepatic ducts and in the gall bladder. A film of a case with several abscess cavities within the liver and air in the gall bladder is especially instructive as the photo of the autopsy specimen appears for comparison. The importance of the visualization of air in the bile ducts is stressed.

In a second paper Berg refers to the newer literature concerning this subject which has come to his attention since the first time he made it public in 1937. He emphasizes that the newer studies of Beckermann are going to improve the possibilities of demonstrating small amounts of gas in the hepatic ducts.—Franz Lust.

MCGOWAN, J. M. AND HENDERSON, F. F.: *Prevention and Management of Pain Following Cholecystectomy. N. Eng. J. of Med., No. 23, p. 948, June.*

Pain following cholecystectomy is due to dilatation of the biliary ducts caused by distal obstruction. Amount of pressure necessary to cause dilatation of the ducts has



been found to vary from 70 mm. to 500 mm. of water. Post-operative pain may be due to disturbances outside the biliary system. In those instances where it is due to diseases of the biliary tract itself post-operative recurrences can be prevented by the prolonged use of T-tube drainage of the common duct. Glyceryl trinitrate is used to relax duodenal spasm. If after three weeks it is found that the T-tube can be clamped off and no pain is experienced with back pressure of 300 mm. of water and resting pressure of less than 30 mm. of water, and roentgenograms show an absence of stones and free emptying of the T-tube, then the tube can be removed. Symptoms of biliary dyskinesia can often be relieved by the daily use of glyceryl trinitrate.—Henry H. Lerner.

TWISS, J. R., CARTEN, R. F. AND HOTZ, RICHARD: *The Determination of Biliary Tract Infection with the Encapsulated Duodenal Tube*. *Ann. Int. Med.*, XIII, 2104, May, 1940.

The results obtained from bacteriological culture of gall bladders removed or specimens obtained at time of surgical drainage has established a high rate of biliary tract infection. Preoperative study of such cases has resulted in a much lower percentage of positive findings and the authors have undertaken their study of a series of 120 patients with the objective of bettering the preoperative diagnoses. Viewing the problem from the other end, greater emphasis can be laid; in preoperative study the gall bladder has been found to be sterile in about 25 per cent of cases studied, while at operation the biliary tract was found sterile in over 65 per cent. Such disparity brings into pertinent inquiry the reasons for the higher per cent of inaccuracies by transduodenal drainage methods. It is relatively easy to understand why higher percentages of positive findings are obtained by duodenal tube drainage—organisms from the pharynx, mouth and stomach afford contaminating organisms that lend to confusion. One of the authors and Phillips in 1936 reported on an improved method of obtaining specimens of duodenal bile by means of an "encapsulated duodenal tube," a tube which Twiss had described in 1933. This tube has a bucket which is covered with a keratin-coated gelatin capsule which is dissolved after the tube reaches the duodenum (provided the contents of the duodenum be alkaline).

The authors present a study of 120 consecutive operative cases in which a preoperative duodenal drainage by the encapsulated method was done. Specimens for culture at time of operation were obtained. The results are interesting: In only 2 per cent of the entire series was there no agreement between specimens obtained at operation and those from the duodenal drainage. After correction of all errors the diagnostic accuracy for the series was fixed at 83 per cent. Sterile cultures were obtained in 75 cases by duodenal drainage and in 74 in specimens obtained by operation. These findings would seem to indicate that bacteriological cultures of duodenal bile obtained under sterile precautions by the encapsulated duodenal tube afford reliable evidence of biliary tract infection.—Virgil E. Simpson.

IVERSON, P. AND ROHOLM, K.: *On Aspiration Biopsy of the Liver, with Remarks on its Diagnostic Significance*. *Acta Med. Scand.*, 102(1/2):1-16, 12 figs., 1939.

Aspiration biopsy of the liver is described. It was done 100 times, but was unsuccessful in 22.5% of the cases. It causes little inconvenience to the patient but is contraindicated if there is a tendency to bleeding. In this way, it is possible to demonstrate acute and chronic inflammatory conditions, tumours, degenerated processes, and biliary obstruction.—J. F. Wilkinson (Courtesy of Biol. Abst.).

BRANISTEANU, D. ET NICOLIESCO, I.: *Sur l'action Cholecystotinctique de l'histamine*. *Bull. Acad. Med. Roumanie*, 8(4):319-324, 5 figs., 1939.

The cystic ducts of dogs anesthetized with chloroform were cannulated, and contractions of the gall bladder were recorded. In 5 dogs, intravenous administration of 5 mg. of histamine was followed by definite contraction within ½-3 minutes. Negative results in 3 cases were attributed to the general anesthesia.—F. H. Snyder (Courtesy of Biol. Abst.).

ROSENBERG, D. H. AND SOSKIN, SAMUEL: *The Azorubin S Test of Liver Function; an Evaluation with Comparative Study of the Bromsulphalein and Hippuric Acid Tests*. *Ann. of Int. Med.*, XIII, 1644, March, 1940.

The multiplicity of liver function, its functional reserve and regenerative capacity have combined to lessen the value of any one test of liver function. None of these tests is of much value in detecting disease of the liver in an early stage. One dependable test of one function is valuable and when taken in conjunction with other dependable tests for other functions does become important.

The authors consider the azorubin S test to have some such merit and think it may be superior to the older, recognized bromsulphalein test by detecting earlier or less advanced stages of chronic liver deficiency. They agree with Eppinger that urinary excretion of azorubin S as a measure of liver function is not dependable. The test offers an opportunity for simultaneous microscopic study of the bile, as well as a liver function test which offsets the patient's objection to a transduodenal drainage. Their comparative observations of the hippuric acid test led to the conclusion that usefulness was limited to the advanced stages of chronic hepatic disease without adequate liver regeneration or to acute diffuse injury.

The method of performing the test is described and the interpretation of the findings based on the determination of color changes in the bile of normal subjects. It is stated that 95 per cent of the dye is excreted in the bile and that the normal appearance time of a deep cherry red color was between 15 and 30 minutes. Their study included 19 cases of cirrhosis, 2 of acute toxic hepatitis, 1 of subsiding acute hepatitis, 1 of fatty metamorphosis of the liver and 4 of early chronic hepatitis. Of the cirrhotic group the test was positive in all, the appearance time of the dye in the bile ranging from 33 to 90 minutes; the bromsulphalein test was positive in 18 of this group, the retention ranging from 10 to 100 per cent; the hippuric acid test was positive in but 6. Of the 4 cases of chronic hepatitis the azorubin S test was positive in all, the bromsulphalein in but one and the hippuric acid test was negative in all.

They stress the value of the crystallographic study of bile and agree with Piersol, Bockus, Shay, Bloch, Lyon and Riegel that a microscopic study of the bile may be more valuable than X-ray study. When both crystals of cholesterol and calcium bilirubinate are found they consider the finding as pathognomic of gall stone disease, and that one makes the diagnosis presumptive.

They conclude with the opinion that the azorubin S test is as reliable as bromsulphalein in hepatic cirrhosis and better than hippuric acid; that it is superior to both in early chronic hepatitis.—Virgil E. Simpson.

PAINE, NORMAN C.: *Acute Pancreatitis*. *California and West. Med.*, 51(5):319-324, 1939.

Acute pancreatitis occurs frequently as a transient colic. In the past, only fulminating and 50% fatal cases of acute pancreatitis have been recognized; 30% of these at autopsy. About 50% of acute pancreatitis is associated with biliary pathology. Intrapancratic pathology is quite frequently the cause. Pancreatic enzyme tests on the blood and urine show a much higher incidence of pancreatitis than was previously supposed.—M. L. Ilsley (Courtesy of Biol. Abst.).



BROCO, PIERRE AND ABOULKER, PIERRE: *Traitement Chirurgical des Plaies Opératoires des Canaux Pancréatiques. Surgical Treatment of Operative Lesions of the Pancreatic Ducts.*

The authors have studied the etiology of the pancreatic fistula in 25 cases. All of them were due to an operative lesion of the head of pancreas. In 22 cases a gastro-duodenectomy was carried out for gastric ulcer. In 2 cases a duodenal diverticulum led to the operation. The lesion of the pancreas took place either during the resection of the floor of the ulcer or during the mobilization of the duodenum. The resection of the ulcer floor penetrating into the pancreas should not be carried out. It may lead to the most serious consequences. The ulcer floor should be left within the organ which it covers. However, sometimes a pancreatic duct opens spontaneously into the ulcer floor, and then the operative procedure cannot be held responsible for the formation of a pancreatic fistula.

The chief pancreatic duct may be endangered by the mobilization of the duodenum, since sometimes the distance between the pylorus and the papilla is only 4 cm. The canal of Santorini may be ligated in such cases. And since in some cases this is the only excretory duct of the pancreas, the consequences may be serious. It is difficult to recognize the lesion during the operation. A small drop of transparent fluid may be seen. If at the same time a lesion of the biliary ducts has occurred, the surgeon will be more prone to look for a lesion of the pancreatic duct, also. The direct reimplantation of the pancreatic duct can be carried out only exceptionally.

The other procedure employed is the invagination of the injured piece of pancreas through an incision into the stomach, the duodenum, or the jejunum.

24 patients were treated immediately after the occurrence of the lesion. 14 of them died; 10 were cured.—Rudolf Schindler.

MAYO, CHARLES W. AND MILLER, JOSEPH M.: *Endometriosis of the Sigmoid, Rectosigmoid and Rectum. S. G. O., 70:2-136, Feb. 1, 1940.*

The purpose of this article is to describe endometrioma so as to distinguish it from carcinoma. Mayo and Miller define an endometrioma as "a tumor or tumors composed of aberrant endometrial cells associated with smooth muscle cells in some situation." It occurs in women between 30 and 49 years of age usually, and symptoms are usually present for a longer time than in inflammatory conditions or carcinoma. Periodic symptoms include constipation, dysmenorrhea, diarrhea, rectal bleeding and pain. Sterility and general discomfort in the lower portion of the abdomen are often associated with this disease.

Statistics and symptoms of 38 cases encountered at the Mayo Clinic are discussed. It was found that an accurate, detailed history and inspection and palpation of the pelvic region are important in diagnosing endometriosis.

The best treatment is conservative resection of the bowel since this will allow the patient to have children. This procedure is especially good if the lesion is malignant, if metastasis is not found and if evidence of endometriosis cannot be found in the pelvis. If the patient is near the menopause age, the more radical treatment of radium implantations or roentgen-ray is employed because it usually offers the possibility of the induction of an artificial menopause and at the same time corrects the endometrioma. If there is an obstruction, a temporary colonic stoma may be made and then radical therapy used.—Francis D. Murphy.

GUY, CHESTER C. AND ROTONDI, ARMANDO J.: *Ovarian Lesions Simulating Appendicitis. S. G. O., 70:6-1100, June, 1940.*

Ruptured follicle or lutein cysts of the ovaries often produce symptoms like those of appendicitis, but if acute appendicitis can be ruled out pre-operatively, many women can be spared an unnecessary laparotomy. Up until this

time, little attention has been given in medical literature to the pre-operative diagnosis of ruptured follicle cyst or corpus luteum hemorrhage, and this study is presented to show the relationship of different factors in making a correct diagnosis.

This study includes the case histories of 52 women operated on with a pre-operative diagnosis of appendicitis. Most of the cases were in the third decade, 25 being the average age. It was found that the relation of time of onset of symptoms to the menstrual cycle was of major diagnostic importance. More than three-fourths of the patients complained of pain in the right lower quadrant between the twenty-first and twenty-seventh days after the last menstruation, while the remaining 23.5 per cent noticed these symptoms on the fourteenth day after the last menstrual period.

Twenty-five of these patients experienced sharp pain, sudden in character, first generalized over the abdomen and then in the right lower quadrant. The remaining patients noticed abdominal pain low in the abdomen of either short duration or of intermittent character. It is believed that vaginal and rectal examination is of definite value in diagnosis.

In most cases, the symptoms were mild and correct diagnosis easily given with expectations for spontaneous recovery. Endocrine therapy may be of value if attacks recur. Some cases showed more pronounced symptoms and clinical findings which simulated appendicitis, tubal pregnancy or other pelvic lesions and called for surgical exploration. If operation seems necessary, every effort should be made to conserve the maximum amount of ovarian tissue.—Francis D. Murphy.

LAKE, NORMAN C.: *Anastomosis Tubes for Resection of the Colon. Brit. Med. J., 2:1052, No. 4147, June 29, 1940.*

To overcome the difficulties of many different types of clamps utilized in resections of the colon, the author mentions Cope as describing an ingenious apparatus in which the tubes themselves form the clamp.

Lake had experimented with an apparatus in which the tubes used to create the anastomosis between the two bowel loops below the level of the abdominal wall. He used this instrument in ten cases which proved to be highly satisfactory, and suggests that it is an improvement in the technic of the Paul operation. Lake describes and illustrates the apparatus and discusses the details of the operative procedures. By this method it emphasizes that in the majority of cases only one operation is necessary for the complete operative procedure.—Maurice Feldman.

TURELL, R.: *The Intestinal Phase in Urologic Disease. III. The Role of the Colon in Urolithiasis. J. Urol., 43:476, March, 1940.*

The literature dealing with the relation of infection to urolithiasis is reviewed. The author believes that pre-existing uroinfection caused by the organisms of the colon bacillus group and inflammatory and suppurative lesions and dysfunction of the anorectocolonic tube are important causative factors in the genesis of urolithiasis in certain cases. The eradication of the foregoing lesions and the correction of dysfunction are an important part of the therapeutic program for the elimination and prevention of urolithiasis with infection caused by organisms of the colon bacillus group.

EHLERT, CH. D.: *Urologic Manifestations of Appendicitis. J. Urol., 43:468, March, 1940.*

The author recently studied the subjective and objective manifestations of appendicitis, which might be confused with those arising as a result of disease of the urogenital tract, (particularly of the lower urinary tract). It is recognized that pathologic elements in the urine occur in patients with appendicitis, but the mechanism of their production is still poorly understood. The urologic mani-

festations of appendicitis are classified as (1) disorders of micturition (frequently and pain of urination, dysuria, and retention of urine); (2) abnormalities in the urine (hematuria, pyuria, albuminuria, anuria); (3) pain or retraction of the right testicle; (4) renal or ureteral colic, and, (5) tenderness in the right costo-vertebral angle.

Hematuria and pyuria are believed to be caused by peri-ureteritis and ureteritis which are brought about by the actual contact of an inflamed appendix with the ureter. Harbin is said to believe that the pyuria is explained by a concomitant pyelitis, and that both appendicitis and pyelitis in some cases are metastatic infections arising from a common focus. Kidney infections in appendicitis may also be caused by lymphogenous ascent of colon bacilli up the ureteral lymphatics. Appendicitis as a cause of pyelitis seems to be an important consideration. Massive pyuria may occur following the rupture of an appendiceal abscess in the urinary bladder.

A short discussion of the other urologic manifestations is also presented.—Robert Turell.

COSACESCO, A., DAVID, N. AND STANESCO, C.: *Les Images Radiologiques de Liquide Libre Intrapéritonéal dans les Péritonites, les Hémopéritonites et les Perforations. X-ray Pictures of Free Intrapertitoneal Fluid in Cases of Peritonitis, Hemo-peritoneum and Perforation.*

Discovery of levels of free fluid in the abdominal cavity by routinely carried out fluoroscopy, especially before abdominal operations, may be of great importance. This radiologic symptom is neither constant nor is it an early symptom, but sometimes it may influence the treatment decisively.

Two levels may be found which suggest the necessity of a double incision. In cases in which an internal hemorrhage may be suspected but in which the surgeon is reluctant to go ahead with laparotomy because of the bad condition of the patient, the fluoroscopic finding of a fluid level in the abdominal cavity may prove the presence of a hemo-peritoneum.—Rudolf Schindler.

LETULLE, RAYMOND: *De l'utilité de l'examen des Selles Pour le Diagnostic Différentiel et le Traitement des Entérites Chroniques de Guerre. La Recherche des Parasites. On the Importance of the Stool Examination for the Differential Diagnosis and Therapy of Chronic Enteritides of the War.*

The author emphasizes the importance of intestinal parasites in serious cases of apparent chronic gastro-enteritides of soldiers. He encourages careful stool examinations in such cases and recommends rather complicated methods of concentration. His discussion of the various intestinal parasites does not bring out any new points.—Rudolf Schindler.

WARREN, MORTIMER, DRAKE, EUGENE H. AND HAWES, RICHARD S.: *Some Observations on the Persistence of the Bachman Skin Test and of Eosinophilia After Recovery from Trichinosis. Ann. Int. Med., XIII, 2141, May, 1940.*

Although the Bachman Skin Test is 10 years old and classed as specific, there is little information in the literature that sheds light on the duration of the test after recovery. One case was found reported by Theiler and associates showing a positive reaction 7 years after infection.\* The authors report their study of an epidemic on 1925 in Portland, Maine, in which 71 persons were known to have eaten the infested pork. Reactions were found in 54, a 1-10,000 dilution of Bachman antigen being used. Three years later they retested 45 of the 52 survivors who originally gave a positive reaction. Of 22 who were clinically ill and reacted positively in 1935, there were 17 who showed a positive Bachman in 1938; this

represents an 85 per cent persistency from the apparent viewpoint of the authors.

The authors conclude:

1. The Bachman intradermal skin reaction remains positive longer than 3 years in the majority of cases of persons having had clinical Trichinosis.
  2. In subclinical Trichinosis with negative skin reaction the test remains negative after 3 years.
  3. Eosinophilia usually absent 3 years after recovery.
- Virgil E. Simpson.

BARBER, HUGH AND OSBORN, G. R.: *The Morbid Anatomy of a Sporadic Case of Infective Hepatic Jaundice. J. Path. and Bact., 49(3):581-585, 1 pl., 1939.*

The death of a man of 38 from a head injury gave the rare opportunity to study the morbid anatomy of infective hepatic jaundice (simple catarrhal jaundice). The essential lesion was found to be in the liver cells, formation of bile ceased. Changes in the lower biliary tree and duodenum were secondary. The condition is contrasted with true catarrhal jaundice which follows gastro-intestinal infections such as dysentery.—Authors (Courtesy of Biol. Abst.).

VEDDER, EDWARD B.: *Discussion of the Etiology of Sprue. Am. J. of Tropical Med., 20:345, No. 3, May, 1940.*

There are several theories regarding the causation of sprue. Ashford's theory of moniliasis is held improbable today. Scott believes that the disease is due to a deficient parathyroid secretion with lack of calcium. The calcium deficiency is more likely a result of disturbed intestinal absorption, rather than the cause. A deficient diet does not explain all the facts.

Sprue should not be looked upon as a tropical disease. It is true that most reports come from the tropics. In a number of cases individuals who had lived in the tropics returned to temperate countries and developed the disease after a latent period varying from one to twenty-five years. Cases have been described in residents of temperate climates who have never visited the tropics.

The pathologic changes are not consistent. Atrophic changes in the mucosa of the small intestine are frequent, affecting especially the glandular epithelium, shrinkage of villi, and valvulae conniventes, and round cell infiltration. The tongue lesions are not always present. The peculiar stools, the emaciation, and macrocytic anemia are characteristic. The anemia is at first normocytic, becoming macrocytic in the later stages. Achlorhydria is not present. Neurologic symptoms in the form of paresthesias, and diminished reflexes occur in a few cases. The blood pressure is around 100, and the basal metabolic rate reduced.

Sprue commences as a functional disturbance of the small intestine resulting in impaired food absorption. Because of the diminished fat absorption, the stools become bulky, fatty and steatorrhea develops. Fermentation of carbohydrates produces gaseous distention and frothy stools. The absorption of calcium and iron is impaired and a disturbance in vitamin absorption also takes place. Hence a vicious circle is set up. The Vitamin B<sub>12</sub> complex is the most essential one lacking in the accompanying avitaminosis. The anemia is probably directly attributable to this lack, which explains the beneficial results of crude liver extract and yeast.

The reason for the intestinal dysfunction is only speculative. Adrenal insufficiency, deficient parathyroid, thyroid, and anterior pituitary have been proposed. Of all the hormonal theories, that of anterior pituitary hypofunction seems the most reasonable.—Phillip Levitsky.

ELMER, A. W., KRASOWSKA, M. AND PTASZEK, L.: *Sucrosuria. A Rare Metabolic Error. Acta. Med. Scand., 101 (4/6):596-608, 1939.*

Exogenous (alimentary) sucrosuria is probably due to the loss of sucrolytic activity of the duodenum; the endogenous form which is independent of the sucrose supply,

\*This does not establish persistence of the reaction that long after recovery, since the patient might well be carrying encysted larvae. (V.E.S.)

is believed to be connected with alterations in the functions of the pancreas and, perhaps, of the liver. Sucrosuria is rare, only 4 cases having been recorded.—J. F. Wilkinson (Courtesy of Biol. Abst.).

LYALL, ALEXANDER: *The Pathology of Chloride Metabolism in Man*. Brit. Med. J., (4110):760-762, 1939.

The normal cycle of chloride metabolism is discussed. Tables compiled from literature and the author's analyses indicate that about 50 to 60 gs. of NaCl is secreted into the alimentary canal in 24 hours. Resorption occurs almost as rapidly as excretion since the plasma Cl conc. does not alter significantly during digestion. The regulation of the Cl content of 12 body fluids is discussed. Renal Cl excretion ceases when plasma Cl is below 520 mg./100 cc. In a case of relieved intestinal obstruction, plasma Cl rose from 467 mg. to 580 mg./100 cc. and urine Cl from nil to 440 mg. After gastric aspiration, plasma Cl fell from 606 mg. to 410 mg./100 cc. and urine Cl fell simultaneously from 310 to 10 mg./100 cc. In Addison's disease the reduction in plasma Cl is correlated with defective kidney Cl retention. Disturbances of Cl metabolism are important in intestinal obstruction, pyloric stenosis, chronic nephritis, edema, obesity, hypertension, and Addison's disease. 25 references are given.—J. B. Paton (Courtesy of Biol. Abst.).

SPIES, T. D., BEAN, W. B. AND VILTER, R. W.: *Adenylic Acid in Human Nutrition*. Ann. Int. Med., XIII, 1616, March, 1940.

The authors have found that certain deficiency diseases are improved when crystalline vitamin supplements are added to inadequate diets, but if the diets were not improved many of these patients continued to have symptoms. They conclude that the essential substances—nicotinic acid, thiamin hydrochloride, riboflavin, oleum percomorphum and Vitamin B<sub>12</sub>—still leave a deficiency.

They report, briefly, their investigations of the properties of adenylic acid on normal persons and those suffering from deficiency diseases. Pellagrins in relapse and others with symptoms believed to be due to a mixed vitamin deficiency were relieved by adenylic acid. The reactions, however, are too severe to warrant its use in human beings in its present form.—Virgil E. Simpson.

DREW, CHARLES R., SCUDDER, JOHN AND PAPPS, JEAN: *Controlled Fluid Therapy with Hematocrit, Specific Gravity and Plasma Protein Determinations*. S. G. O., 70:5-859, May, 1940.

The authors present four tests as to the state of hydration in seriously ill surgical patients. They are (1) determination of the percentage of cells in venous blood; (2) determination of the specific gravity of the whole blood; (3) determination of the specific gravity of the plasma and (4) calculation of the plasma protein content by means of a simple formula.

These tests are of value in determining the degrees of water loss, water plus protein loss, the onset of shock, differentiating shock due to simple circulatory collapse from shock complicated by hemorrhage, detecting dehydration in the presence of anemia, predicting the approach of an edema level of proteins and directing treatment more rationally for the alleviation of any of these conditions.

In simple dehydration, a rise in the cell volume, whole blood and plasma specific gravity and plasma protein percentage occurs. Treatment consists of giving fluid until the elevated values approach normal. In some cases, as shock, treatment is more complicated. Treatment must attempt to overcome (1) severe arteriolar and venular spasm; (2) capillary paralysis and dilatation and (3) the great loss of circulating blood volume. Hypertonic sodium chloride, suprarenal cortical hormone (eschatin) and blood transfusions are valuable treatments.

In hemorrhage there is usually a fall in the specific gravity of the whole blood, drop in cell volume, and plasma

specific gravity changes are less marked. Blood transfusions constitute treatment. When there is loss of both fluid and protein, the problem is more difficult. The extreme hemoconcentration and shock, if present, must be combated by means of adequate fluid administration, yet the lowered protein concentration must not be reduced to the edema level.

When acute changes take place in chronic disease, all tests are necessary. Sudden water loss is shown by an increase in the weight of the plasma. The protein values should be reduced to approximately normal levels and the cellular elements of the blood restored. Impending edema is shown by a gradually falling plasma protein level and since water-logging of tissues is detrimental in surgical conditions, repeated plasma protein determinations should be made.

In cases of hemoconcentration in which the hematocrit reading is over 60 per cent cell volume, large quantities of hypertonic solutions are contraindicated. In the severely ill, it might be wise to withhold fluids until the severe spasm of the peripheral vessels is relieved and the sequestered blood in the paralyzed peripheral capillaries returns to circulation.—Francis D. Murphy.

CARPENTER, THORNE M.: *The Combustion of Carbohydrates in Man After Ingestion of Common Foods*. J. Nutrition, 19:423, 1940.

The increases in carbohydrate combustion during the 3 hours following food ingestion were greater, the greater the amounts of reducing and hydrolyzable sugars in the foods, and smaller the greater the amounts of starch or fat in the foods. The boiled vegetables that may be characterized as sweet (parsnips, beets, carrots and squash) caused the greatest increases. Nuts, rice, macaroni, white potato, and bread caused the smallest increases. The combustion of carbohydrates was greater when carrots were eaten raw than when eaten cooked, but the picture was the reverse with white potatoes. The increase in combustion was sudden and marked but quickly over with cane sugar and dates. That with glucose was slower and less marked but lasted longer. With parsnips the readily digestible carbohydrates were 'burned' first; subsequently the more complex carbohydrates were liberated and made available. With nuts the increases in carbohydrate combustion were small but continuous; they were somewhat greater with cashew nuts than with other nuts—A. E. Meyer.

FREE, ALFRED H. AND BING, FRANKLIN C.: *Wheat as a Dietary Source of Iron*. J. Nutrition, 19:449, 1940.

The iron content of eleven samples of American grown wheat varied from 2.90 to 4.87 mg. per 100 gm. and the average was 3.94 mg. The proportion of the total iron in the form of ionogenic iron ranged from 73 to 88%. Within these limits the ionogenic iron is a constant proportion of the total iron. By means of biological assays with anemic rats it was shown that the iron of wheat is fully as available to the organism as an equal amount of iron in the form of ferric chloride. About one-half of the iron of ferric chloride or of finely ground whole wheat is retained by the anemic rat. In view of the results of the feeding tests it is difficult to interpret the values obtained with the chemical method for the estimation of ionogenic iron.—A. E. Meyer.

MACY, ICIE G., HUMMEL, FRANCES COPE, HUNSCHER, HELEN A., SHEPHERD, MARION L. AND SOUDERS, HELEN J.: *Effects of Simple Dietary Alterations Upon Retention of Positive and Negative Minerals by Children*. J. Nutrition, 19:461, 1940.

Nine children were the subjects of metabolic study ranging from 20 to 55 consecutive days for each child. Chemical analyses demonstrate that a conservative sub-

# Factors in the Diagnosis of Intestinal Protozoa in Man and in the Interpretation of the Findings

By

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THERE is a growing interest in the problem of protozoal infection, but the subject still falls far short of the position it deserves. Even when interest is manifested, the laboratories are often impeded by inadequate training of personnel and unfit or insufficient material to examine. This fault arises from a failure to recognize four factors: (1) the incidence of protozoal infection in non-tropical zones, (2) the possibility of protozoa causing symptoms other than diarrhea, (3) the difficulty of finding and identifying organisms, and (4) the necessity of examining material which has not been rendered unfit by improper collection or the inadvisable use of drugs.

The records of the search for protozoa in over 3500 specimens from 1212 persons are used as a basis for

pond with the figures of true surveys from all parts of the country and indicates the frequency of protozoal infection in non-tropical zones. The reports of numerous authors on the incidence of *Endamoeba histolytica* have been averaged by Craig, on the basis of which he has estimated the incidence to be 10% for the whole country (6). According to Andrews (1), there is a geographic variation: "Available evidence seems to indicate that amebic infection is least prevalent in the northeastern quadrant of the country and is most prevalent on the Gulf Coast with intermediate incidence on the Western Coast." It is clear that over the entire United States each physician should heed the paragraph of Dr. James (12): "If one works in areas in which *Endamoeba histolytica* infection is present and wishes correctly to diagnose and treat the many varieties of 'stomach trouble' which constantly present themselves, one must be prepared to recognize amebas in the stools and to differentiate *Endamoeba histolytica* from the three other amebas commonly found and frequently associated with it in the same stool: *Endamoeba coli*, *Iodamoeba butschlii* and *E. nana*."

TABLE I

Protozoa	Individuals Positive	
	Number	Per Cent
<i>E. histolytica</i>	65	5.4
<i>E. coli</i>	101	8.3
<i>E. nana</i>	62	5.1
<i>Iodamoeba williamsi</i>	3	.2
<i>Giardia</i>	56	4.6
<i>Chilomastix</i>	21	1.7
<i>Trichomonas</i>	33	2.7
<i>Embdomonas</i>	3	.2
Total cases		1212
No. of positives		247
General incidence		20.4%
Total days examined		3619
Days examined per case		3
Single infections		167
Multiple infections		80

discussion of the four points mentioned. To conserve space, some of the conclusions are not accompanied by the data. A distinction between specimens and days examined has been made in this report: A specimen day may include several specimens passed on that day. The records show that, if one defecated specimen contains a protozoon, all specimens passed that day will also contain the protozoon, although the concentration may vary considerably.

## INCIDENCE

The incidence in the group of patients discussed in this paper is shown in Table I. This table does not represent an actual incidence for any locality, since the group is not properly balanced, but it does corres-

## PROTOZOA AND DISEASE IN GENERAL

With the exception of *Endamoeba histolytica* among the Amoeboae, *Balantidium coli* among the Ciliata, and *Isospora hominis* among the Coccidia, there is no universal opinion as to the pathogenicity of human intestinal protozoa. Excluding these, there is no conclusive proof that actual invasion of the bowel ever occurs in the living, nor has there been demonstrated any means by which the protozoon could attack the tissues of the host. *Trichomonas* was discovered in the wall of the gut in five cases by Wenyon in 1920 and has been reported to have been found in the blood in autopsy material, but there was a question of post-mortem infiltration due to the viability of *trichomonas* (21). *Trichomonas hominis* is known to ingest red blood cells occasionally, and in one case of this series in which red blood cells were plentiful, many of the *trichomonas* present contained red blood cells. The ingestion of red blood cells in itself can not be accepted as indicating pathogenicity.

It is known that protozoa of all types occur frequently in diarrheal stools and that improvement follows their successful removal often enough to give some basis to the claims for pathogenicity. Whether these protozoa actually produce enteritis, or whether they live as harmless saprophytes in the intestinal tract and are discovered in these cases, because the increase in fluid content favors their growth and more rapid peristalsis brings them down, is unknown. Likewise, it is impossible to say whether improvement after treatment occurs because the organisms have

Read at the Annual Session of the American Gastro-Enterological Association at Atlantic City, N. J., June 10, 1940.

been destroyed or because some unknown factor has been combatted.

Giardia is not only suspected of affecting the bowel, as are the other protozoa, but is also thought to produce biliary pathology. This belief apparently derives from the discovery of the flagellate in material obtained from duodenal drainages and from reports that it has been found in the bile of postoperative gall bladders. Since the duodenum is the normal habitat of giardia and duodenal drainages are commonly done only on patients with symptoms referable to the biliary tree, further proof of the pathogenicity of giardia is needed. This has become important since atabrine, which sometimes results in untoward reactions, has been shown to be a specific for this organism (18).

Trichomonas is supposed to produce vaginal irritation without actually invading the vaginal wall. Since no consistent difference between trichomonas in the vagina and trichomonas in the stool has been discovered, it might be concluded that this protozoon could also produce irritation in the bowel without demonstrable lesions.

It seems unwise to state dogmatically that these supposedly harmless protozoa have no effect on the host regardless of circumstances. If protozoa are present in the stools of persons suffering with gastrointestinal irritation, if no other cause can be found, and if symptoms persist after other treatment has been tried, it is good practice to remove them.

There is even debate concerning the pathogenicity of *E. histolytica*. The question is not one of treatment, for this is indicated because of potential danger, but of the role played by the protozoon at the moment of discovery. The arguments for the occasional benignity of *E. histolytica* are based primarily on two observations: (1) that a certain percentage of any series of people infected with *E. histolytica* will deny symptoms (Craig's estimate of 33% seems fair (6)), and (2) that a certain percentage of any group of infected patients having symptoms of disease of the large bowel do not appear to be benefited by the removal of the parasites (5, 6, 11, 14). These observations do not seem to support adequately the conclusion that the host is not being damaged. In the first place, the bowel is notorious for its unreliability of symptoms. It has been shown that patients with *E. histolytica* infection may have extensive bowel ulceration or an insidious impairment of health without being aware of it (5, 6, 13). There may be damage to the mucosa without ulceration or obvious gross defects (13, 14). In the second place, *E. histolytica* may not have been the sole cause of the trouble but may have been merely contributing to the distress of an otherwise nervous, irritable and unstable patient. The benefit of treatment may not be apparent immediately, even when all amebas have been removed during the first course of amebicide, as it sometimes takes months for old chronic ulcers to heal. Furthermore, I can find no record of an autopsy of a known *E. histolytica* carrier where demonstrable lesions were not found, nor have I seen any quoted. Neither have I found a patient infected with this protozoon in whom disease or disturbance of the colon could not be demonstrated. In both survey and private groups, some of those harboring *E. histolytica* denied large bowel symptoms, but when there was opportunity for careful study, some colonic disturbance could be shown.

There has been a great deal of discussion of the reasons for the variation in severity of symptoms. James (13) suggests that *E. histolytica* may live in the lumen of the bowel and invade it to a serious extent only at intervals; in between these times host and parasite may maintain a balance. The deciding factor in invasion may be an increase in virulence of the organism or a decrease in the resistance of the host or both. There is no definite proof that *E. histolytica* may change in virulence, but there could be a variation from time to time in the quality and quantity of its main offensive weapon, the histolytic toxin (14). One interesting feature of the *E. histolytica* in this series is that there actually seemed to be some morphologic variation between the protozoa isolated from frank dysenteric patients and those obtained from the patients with minimal symptoms: The latter seemed more sluggish, smaller, browner in color, and had larger granules. James also mentions that the organisms seemed smaller in the milder cases (13). I have

TABLE II

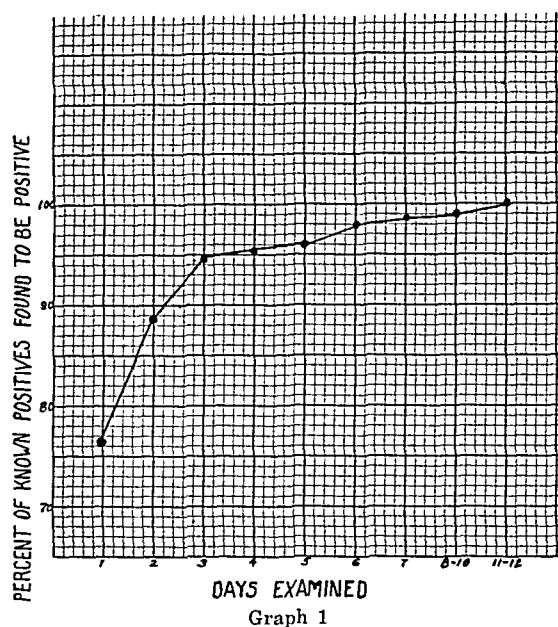
No. of Specimens	1	2	3	6
Dobell (8)	1/3		1/2-2/3	
Kessel and Svenson (17)	44.0% <i>E. histolytica</i> 47.0% <i>E. coli</i> and <i>E. nana</i> 12.0% Giardia			
Milam and Meleny (17)	50-60%		Increased by 23%	
Hoek and Stiles (3)	1/3-1/2			
Carter et al (16)	33.4% <i>E. histolytica</i> 10.5% <i>E. coli</i> 18.7% Giardia			
Faust (9)	10.0% Trichomonas 47.0% <i>E. coli</i> Giardia			
James (12)	1/3		1/2-2/3	90%
Survey (12) Fresh	0%	90%		
Practice (12) Stain	75%			

heard Dr. Walter Palmer mention this in several discussions.

The available evidence indicates that in any patient infected with *E. histolytica*, regardless of the presence or absence of large bowel symptoms, the large bowel is probably being damaged, and the number of protozoa in the stool is not a reliable guide to the extent of the involvement. The failure of large bowel symptoms to subside immediately following treatment can not be taken as proof that the infection was not contributing to the general poor health. The indications are also clear that a search for *E. histolytica* should be made in any patient in whom chronic infection or large bowel pathology could contribute to the picture.

#### DIFFICULTY OF FINDING AND IDENTIFYING ORGANISMS

Protozoological diagnosis requires the highest type of microscopic technique. A skeptical attitude in this field toward reports in the literature as well as in one's laboratory is justified. There is no substitute for long



training under a competent protozoologist. It can be stated flatly that reports coming from a technician who lacks long and specific protozoological training, regardless of his competency in other microscopic fields, had best be discarded and conclusions drawn from clinical observations alone.

The establishment of a diagnosis, the determination of the effect of treatment and the recognition of recurrence depend on compensation for the fact that protozoa are not present daily in the stools of infected persons. The numbers found vary greatly from day to day. Various authors have estimated the relative value of single and multiple stool examination as illustrated in Table II. These figures are based mainly on unconcentrated and unstained material.

In this survey there were 247 patients with proven infections whose stools were examined on 1025 days. In order to determine the frequency of positive days, only the records of 168 persons whose feces were examined three or more days were analyzed. These re-

sults are given in Table III. Protozoa were found in the feces 70% of the time in the whole group. However, when only one organism was found, it was present 66% of the days. An analysis of the individual organisms in the single infection group shows that an average of 64% of days examined were positive, varying from 50% of *E. histolytica* infections to 81% in *E. coli*. In the multiple infections, protozoa were found 78% of the days, but in 39% of the days one or more of the protozoa known to be present in the bowel were not found. Of 60 patients with multiple infections who were examined on three or more days, in only 11 did all of the specimens contain all organisms known to be present; in 13 no specimen contained all. Of this group 38% of the specimens contained all the protozoa. In 42% one or more protozoa known to be present was missing, and in 20% no protozoa were found. The analysis of the individual organisms found in the multiple infection groups shows that the percentage of occurrence differs slightly from that of the single infection group but averages at about 68% positive days. There was no constancy in variation: Organisms occurred on successive days, on widely separated days or in runs of positive days.

The graph illustrates by accumulated percentage the number of infections found to be positive on the first day, second day and so on. Seventy-six per cent of known infections were discovered at the first examination and by the sixth examination 98% had been discovered. Since all infected persons with more than one examination are included, the figures do not represent true efficiency, because there were undoubtedly undiscovered multiple infection, particularly in those persons having only two or three examinations.

The effect of these variations on the incidence as reported in surveys can be seen when the general incidence listed in Table I is broken down into groups of persons whose feces were examined on one day, two days, three days, etc. (Table IV). The incidence tends to become greater with the increasing number of days on which specimens are examined. The percentage of multiple infections discovered also increases. It is to be particularly noted that the incidence of *E. histolytica* is most affected. It seems wise at this point to state that in this study the number of specimens ob-

TABLE III

	Number of Patients	Days Examined	Days Positive	Days Negative	Per Cent Positive	Days When One or More Organ. Were Missing
Entire group	168	920	650	270	70.7	
Single infections	108	575	381	194	66.4	
Multiple infections	160	342	266	76	77.8	39.2%
Individual organ. In single infections						
<i>E. histolytica</i>	16	97	49	48	50.1	
<i>E. coli</i>	30	128	104	24	81.3	
<i>E. nana</i>	22	141	92	49	63.6	
<i>Giardia</i>	17	77	49	28	63.6	
<i>Chilomastix</i>	5	27	16	11	59.3	
<i>Trichomonas</i>	18	105	71	34	67.6	

tained from the patient was determined by the patience of the observer and the examinee rather than the positive or negative results of examinations. However, the increased incidence in the higher groups was somewhat influenced by greater interest in actual diarrheal cases, and the discovery of *E. histolytica* in early specimens sometimes terminated the search for protozoa.

The effect of these variations on the individual case is even more important. In a survey if a sufficient number of cases are examined, the error tends to balance, but when confronted by an individual patient and the necessity of knowing definitely whether he is or is not infected with protozoa, many stool examinations are imperative. Three stool examinations are often accepted as an adequate test for the presence of protozoa; six examinations are universally conceded as the optimum number for a survey. Table V shows the results of the application of this rule to individuals. In 144 people with more than three successive daily examinations, nearly 10% of the single infections would not have been found, had examinations ceased after the third day. Additional protozoa were found after the third day in 31% of the multiple infections. Again attention is called to *E. histolytica* in this chart: Over 21% of the infections by this protozoon were not discovered until after the third day; in one patient the organism was not found until the fifteenth day. In 56 patients who were examined more than six successive days, 12% of the single infections would have been missed, and one or more protozoa would have been overlooked in 17% of the multiple infections.

Of the numerous enrichment methods, two were utilized routinely in this study: the method of levitation (zinc sulphate) described by Faust et al (10), and a variation of the standard centrifuge method. The zinc sulphate levitation method cannot be praised too highly for its efficacy in the discovery of ova. It proved practical for this purpose in a simplified version. However, the full technique must be carefully carried out for the detection of cysts. This proved to be too cumbersome for routine use. The best practical method of enrichment for aid in the search of cysts is by centrifuging. For this purpose it is important to use a fecal suspension of such density that, after

centrifuging and decanting the supernatant fluid, the residue can be examined without further dilution.

There were 44 specimen days of positive patients on which unconcentrated material alone was used, and 68% were found to be positive. There were 123 specimen days of positive patients on which concentrated material was examined and 69% were positive. Of 75 specimens examined directly and after centrifuging, in only one was the protozoa found in the concentrated and not in the unconcentrated, and there was one in which the reverse was true. Of 268 positive specimens enriched by centrifuging and levitation, protozoa were found in the centrifuged material and not in the floated in 74 specimens. In only three was the floated material positive when the centrifuged was negative.

Since the habitat of protozoa is in the higher portions of the bowel, the number decreases toward the rectum. Therefore, on days when few organisms can be discovered in the stool, more can be found after obtaining material from higher in the bowel by purge, by colonic irrigation or by lavage of the sigmoid stream through the sigmoidoscope. Paulson and Andrews (20) called attention to this use of the sigmoidoscope and by using sigmoid lavage increased their total protozoal incidence from 13.7% in defecated specimens to 46.3%. The records on the infected patients in this series confirm this finding. Table VI demonstrates the effectiveness of the purge and the proctoscope in discovering organisms. Proctoscopic lavage increases the general incidence from 11% (Table IV) to 30%. The increase would have been more marked, had the sigmoid stream been reached in all cases. However, even when utilizing all of these devices, there are days when no organisms can be found in concentrated material obtained from high in the bowel; therefore, there must be at times a general diminution of the number actually present in the bowel. The reason for this subsidence of infection is not clear. Since analysis of multiple infections shows that the organisms vary more or less independently of each other, the cause does not appear to be conditions in the bowel itself. The records in this series of positive cases show frequent variations in the pH (ranging from below 4.5 to above 8), and there was apparently no relationship between the pH and the presence or absence of protozoa. Diet, of course, has

TABLE IV

Exam. Per Patient Protozoa	1	2	3	4	5	6	7-9	10-12	12+
	Incidence Per Cent								
<i>E. histolytica</i>	2.3	4.0	6.1	5.6	6.0	6.5	11.9	38.9	14.3
<i>E. coli</i>	2.8	10.2	11.9	9.8	9.0	10.9	16.6	16.7	14.3
<i>E. nana</i>	2.0	8.0	4.0	4.0	7.7	8.9	8.3	11.1	21.4
<i>Giardia</i>	3.0	4.0	6.5	6.3	9.0	0.0	10.7	5.6	0.0
<i>Chilomastix</i>	1.2	1.1	1.8	0.8	1.5	2.2	4.8	5.6	0.0
<i>Trichomonas</i>	1.2	2.3	2.5	2.4	7.7	6.5	4.8	11.1	7.1
<i>Embadomonas</i>	0.3								
<i>Iodamoeba williamsi</i>			0.7					5.6	
Gen. incidence per cent	11.2	21.6	23.5		29.9			55.6	
Mix. infections per cent	1.4	7.4	7.6	17.5	8.3	32.6	38.1	17.1	42.9
Total patients	347	176	277	126	67	46	84	18	14

some effect. Hegner demonstrated that many flagellates will disappear on a high protein diet. This was observed in some of these cases, but no connection with ordinary variation in diet could be found, and the amebas did not seem to be affected. Solidity and fluidity of the stool seemed to determine whether trophozoites or cysts were present but not the frequency of

with a few exceptions. I have kept cysts for two years in this solution without deterioration. In using preserved material, one must be certain that the stool collected is formed, that it is placed in formalin immediately, and that further specimens are collected if the cysts are not intact. If the limitations and uses of this method are kept in mind, it will prove extremely valuable.

TABLE V

	No. of Patients	Found After Third Day	Additional Protozoa Found After Third Day
<b>SINGLE INFECTIONS</b>	105	5 4.5%	
E. histolytica	10	3	
E. coli	8	0	
E. nana	12	2	
Giardia	7	0	
<b>DOUBLE INFECTIONS</b>	28		4 12.5%
E. histolytica	10		3
E. coli	8		0
E. nana	12		2
Giardia	7		0
<b>3 OR MORE PROTOZOA</b>	11		5 31.2%
E. histolytica	8		1
E. coli	10		1
E. nana	6		0
Giardia	5		1
<b>TOTAL</b>	144		14 9.7%
E. histolytica			21.0
E. coli			5.5
E. nana			9.6
Giardia			5.0

appearance or the numbers. The flagellates not having cysts (trichomonas) are not commonly present in a solid stool.

To summarize, given competent examiners, there are days when one is unable to demonstrate intestinal protozoa in patients known to be infected. If only a single examination can be done, the surest method is to obtain material following a purge, to obtain it from the sigmoid stream, or both. Even then, this single examination is inferior to investigation of a large series of defecated stools.

Recognition of the independent variation of the organisms is important, because the discovery of one or more organisms, even in large numbers, does not remove the need for examination of further specimens. In private practice, it is often impossible to collect specimens for a sufficient number of days, and I wish to recommend the use of preserved material. I have had considerable experience with specimens preserved in 5% formalin both in private practice and survey work. Comparison of all figures in this paper with figures of similar groups of preserved specimens shows that the latter is slightly inferior to fresh material in every way, but the increased number of days permitted by the method compensates for the difference. Trophozoites usually disintegrate, but cysts preserve well

# THE NECESSITY FOR EXAMINING SUITABLE MATERIAL

It is not unusual for the physician to defeat his own attempts at diagnosis by not furnishing the laboratory with suitable material. The rapidity with which trophozoites may deteriorate in soft or liquid specimens is astonishing. In one case of this series, *E. histolytica*, which were plentiful at the time the feces were passed, had completely disintegrated within fifteen minutes. Liquid stool examinations must not be relied on if the specimen cannot be examined immediately.

The presence of oil in the stool also renders examination unreliable. The globules of oil not only obscure the field but catch the eye of the observer and detract from the chances of seeing protozoal cysts.

The third major cause of unfit material is the use of barium or bismuth. It is not unusual for a physician to give paregoric and bismuth at the outset of a diarrhea or to order a gastro-intestinal series or barium enema before stools are examined. Andrews and Paulson (2) have pointed out not only that examination of feces containing barium will result in a reduction of the number of diagnoses, but have shown experimentally that the ingestion of barium sulphate will result in such a reduction in the number of intestinal protozoa per unit volume of stool as to make diagnosis impossible. This reduction occurs primarily in the amebas and may last from one to two weeks. These authors did not test bismuth, but from my own experience bismuth has an even greater effect. This diminution in the number of protozoa results partly from dilution by the barium, but I believe that actual

TABLE VI

	Purge	Proctoscopic Lavage
Defecated specimen positive Purge or lavage negative	2	3
Defecated specimen negative Purge or lavage positive	1	1
Defecated specimen positive Purge or lavage positive	40	23
Total positive	43	27
Total examined	133	91
Per cent positive	32.3	29.7
Additional protozoa found in defecated specimen	10	2
Additional protozoa found by purge or lavage	1	1

traumatic destruction of the amebas may occur. We placed in two soft rubber tubes equal quantities of similar mixtures of protozoa and normal feces and of protozoa and feces containing barium from a previous day's barium meal. By rolling these tubes at intervals, the cysts in both specimens could be destroyed. By more gentle rolling, it was found that the cysts in the



barium filled specimen were broken up more readily than in the other. *E. histolytica* cysts were damaged much more easily than any others, an observation similar to that of Andrews and Paulson, who noticed that the effect of barium on *E. histolytica* seemed more marked.

### CONCLUSIONS

1. The incidence of intestinal protozoal infection in all parts of the United States is such that each physician is confronted frequently by infected persons.
2. The exact relationship of these parasites to the host is not yet proven.
3. Proper statistical evaluation of protozoal infection and assay of the part played by a protozoan in the symptomatology of a patient depend on compensation for the fact that protozoa are not present daily in the stool of infected persons.
4. Material may be rendered unfit for examination by improper collection or by giving the examinee oil, barium or bismuth.

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### DISCUSSION

**DR. MOSES PAULSON** (Baltimore, Md.): Dr. Borland comes to his task peculiarly well qualified; after having left Harvard, he spent some years at Johns Hopkins, where he became interested in parasitology. He is one of the relatively few men who having left large medical centers to go to smaller communities, continues to pursue his investigative interests.

He has attempted to point out, I think, that interest in parasitology ought no longer be relegated to those engaged in tropical medicine. By virtue of the ease of travel, because of the fact that so many of us no longer eat ex-

clusively within our own households, and also because of the abominable practice—in some places—of using human feces as fertilizer, protozoan infestations and infections have been disseminated. It has now become a problem for the clinician in the temperate zone. Dr. Borland has pointed out the marked difficulties encountered in detecting these protozoa, making special training essential.

I had occasion to read his paper and because of lack of time I know that he had no opportunity to stress several important facts that the clinician must keep in mind; they are confirmatory of earlier studies by Andrews and myself: First, barium sulphate given for roentgenologic examination will reduce the incidence of intestinal protozoa to a marked degree, by dilution and through trauma. Secondly, the administration of bismuth for therapy, prior to parasitologic examination, will reduce incidence to even a more marked degree. Thirdly, it is desirable to secure saline-purged specimens as well as to use the sigmoidoscope to secure material from above the rectum or directly from the source of involvement in the distal colon. This results in ready examination and an increased incidence of parasites.

The high incidence of parasites he found in Florida will be encountered in practically all communities of the temperate zone. When our laboratories continue to report to us very low parasitological incidences, it is merely an index of the inadequately trained personnel. In Baltimore, among the poor, whose hygienic conditions in many respects are much better than the better-to-dos (this is a matter I can't go into here), our incidence was 43.3 per cent when material was secured from the sigmoid by the sigmoidoscope as compared with 13.7 per cent secured from defecated specimens from the identical source. There is no reason to suspect the same thing isn't true in other large population centers.

Finally, there is one point upon which I must disagree with Dr. Borland, and that is, I think, in the light of present knowledge, that one cannot state that a parasite bears a direct causative relation to symptoms unless subjectively and objectively there is complete—not partial—relief upon eradication of the parasite.

**DR. HORACE W. SOPER** (St. Louis, Mo.): I wish to say that I consider this an extremely valuable paper and that I concur in the Doctor's conclusions. Not only are the amoeba coli pathogenic but many of the flagellates at times develop pathogenicity because of lack of resistance on the part of the host. For many years, in fact ever since I have been in gastro-enterology, I have followed two rules, viz., no matter what the patient's complaint I make a feces analysis and proctosigmoidoscopy. Therefore, I frequently diagnose cases of catarrhal colitis which are ordinarily overlooked.

There is just one point about diagnosis: In addition to your saline cathartic prior to examination for histolytica particularly, there is one thing I have found by proctosigmoidoscopy, namely, that the smear secured from the mucus that collects in the lower ampulla just above the internal sphincter has often given me the organism when feces analysis and salines have failed.

**DR. ERNEST H. GAITHER** (Baltimore, Md.): I desire to emphasize and support the statement made by Dr. Borland regarding the value of multiple examinations of the stools, looking toward the discovery of the *Endamoeba histolytica*.

At the office for some years past our routine has been to have the patients come early in the morning, about eight o'clock, at which time there is administered a large dose of magnesium sulphate, and the fresh stools are collected and examined in the warm state; however, it should be stressed that the examinations be made by those particularly skilled in this work.

As an example of the importance of multiple examination, I desire to cite the following case. A patient who

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was suffering with a marked diarrhea of some weeks standing which had been treated as a simple diarrhea and irritable colon. He was given the magnesium sulphate. Four stools were examined in the morning by the technician, and she found cysts. She did not feel quite satisfied and had the patient come in later in the afternoon. The request was made for another specimen and the patient obliged us by giving a fluid stool, at which time very active *Endamoeba histolytica* were found. I desire again to emphasize the importance of multiple examinations of fresh stools in quest of the *Endamoeba histolytica*.

DR. JOHN TILDEN HOWARD (Baltimore, Md.): If I have understood Dr. Borland correctly, he believes that *Endamoeba histolytica* is an obligate tissue parasite and always produces a symptom of one kind or another in those who harbor it. How does he explain the cultivation of the parasite, as Andrews and Atchley pointed out, on a medium free of blood cells and serum, and in which the parasite ingests starch? Certainly the lesions produced by *Endamoeba histolytica* must be sometimes minimal, for Andrews and Atchley got negative benzidine tests on the stools of twelve out of thirteen carriers. We must remember that Dr. Hegner could find no gross or microscopic lesions in the bowels of four monkeys which he had made carriers and that amoebic ulceration of the colon is rarely found at routine autopsy, though from five to ten per cent of the population is infected. For two or

three years, I, personally, have been looking for the death of a carrier, who came to autopsy, and have been unable to find one.

This data, the failure of Paulson and Andrews to get lasting relief from amoebicidal therapy in their reported treatment of carriers, and my own observations that vague, gastro-intestinal symptoms were permanently relieved in only about 25 per cent of carriers by eradication of the parasites, make me feel that *Endamoeba histolytica* is not an obligate parasite, and that it is not always the cause of symptoms.

However, everyone will agree that all known carriers of the parasite should be rid of it for their own safety and for public health reasons.

DR. JAMES L. BORLAND (Jacksonville, Fla.): I want to thank the discussers. *Endamoeba histolytica* is obviously not an obligatory parasite. In answer to Dr. Howard, I should like to point out that most pathologists do not watch carefully for evidence of this disease and in addition, as Dr. James has shown so beautifully, extensive damage may exist in the bowel without much gross change in the specimen. It may be that with increasing attention, we will be able to find carriers without demonstrable bowel damage. To date there has been no such report, and I think it is wise to regard any present infection of *Endamoeba histolytica* as causing disease and contributing to some extent to the symptoms.

## Acute Ulcerative Esophagitis\*

By

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ACUTE esophagitis is frequently discovered at necropsy as an incidental finding without any symptoms in the history to suggest its presence. Most of the literature on the subject appeared in journals of laryngology or pathology, which is so voluminous that only a few references will be cited at this time.

Butt and Vinson (1) found 213 cases of esophagitis in 3,032 autopsies over a period of six years. One hundred sixty-three of these were of the acute ulcerative type. One hundred fifty-nine cases followed operative procedures. Some type of infection such as pneumonia, peritonitis or cholecystic disease was present in 128.

Bartels (2), in a clinical study of 82 cases of acute ulcerative esophagitis found in an examination of 6,000 specimens at autopsy, that 45 followed operative procedures, and 34 out of these 45 had gastro-intestinal diseases involving the colon, biliary tract or stomach.

Mosher (3) studied 100 specimens of all types of esophagitis at autopsy and found acute inflammation following cavernous sinus thrombosis, infectious thrombophlebitis, mesenteric thrombosis, general peritonitis, acute pyelonephritis, cholecystic disease and pneumonia. While Penner and Bernheim (4) reported but one case of acute esophagitis in a series of four cases of acute post operative esophageal, gastric and

duodenal lesions, it is pertinent to include their report because of a theory as to etiology that they have propounded which could also account for ulcerative colitis (5) found by them after operative procedures.

This report deals with 26 cases of acute esophagitis, 20 in adults and six in infants. The problem in infants may be somewhat different, because the condition may be due to thrush, as Ebbs (6) reported, or to a complication of a congenital lesion as esophageal narrowing. This was found twice in our cases. One child died of a fulminating hemorrhagic encephalitis, and two others of severe toxemia with vomiting and diarrhea in the first two weeks of life. Severe acute membranous esophagitis was found in all. Diffuse severe icterus and kern icterus were found in two.

The ages of the adults reached from the third to the eighth decades; six of the patients being in the seventies. Six were males and 14 females. Fourteen had been operated upon, ten for affections of the gastro-intestinal tract, as peptic ulcer, biliary tract infection, intestinal obstruction, and acute appendicitis. Of the non-surgical patients, two died of acute coronary occlusion, one of congestive heart failure and tracheobronchitis and one of carcinoma of the pancreas with duodenal invasion, and one of subphrenic abscess and gastric ulcer complicating prostatic disease. The frequent association of peptic ulcer with acute ulcerative esophagitis has been noted by Butt and Vinson, Bartels and others. There is a large number of cases

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cited in the literature of chronic esophagitis, some with peptic ulcer, associated with ulcer of the stomach or duodenum. This type is not under consideration here. Butt and Vinson (7) believe that most of the lesions described as peptic ulcer of the esophagus are in reality persistent acute ulcerative esophagitis. In one of the present series peptic esophagitis was found. However, peptic ulcer of the stomach or duodenum was found in six cases.

Little seems to be known about the etiology of this



Fig. 1. Acute esophagitis. Note the hemorrhagic discolorations of the mucosa.

form of esophagitis. Butt and Vinson believe that the trauma produced by an indwelling Levin tube for decompression of the abdomen, or irritation from vomiting are important causes. Forty-six per cent of their patients had been intubated or vomited excessively. Esophagitis is not thought by them to be an agonal episode, but begins to develop several days before death. In our series 11 out of 17 patients operated upon were intubated. Seven vomited and five were intubated and vomited. Of three surgically treated patients in whom chronic esophagitis was found at autopsy and not included in this series, one vomited excessively, one had been intubated and also vomited. A large amount of sanguinous fluid was obtained by a tube in two patients who had not vomited. In some patients the tube was inserted for a single aspiration, in others the tube was in place for varying periods of a few hours to 24 hours.

It is not unreasonable to accept the statement that both vomiting and intubation may play a part in the production of acute esophagitis. Vomiting, however, is extremely common post operatively. Acute esophagitis is comparatively rare. The streaking of the esophagus, ascribed by some to the tube, is not necessarily due to the tube. This has been noted by others, particularly Bartels, who does not believe that intubation is an etiologic factor, and has found similar streaking of the esophagus in cases where intubation was not used. Intubation was used in about a third of his 82 cases. We have all seen a large number of patients who either had vomited excessively or had been intubated, and did not show any evidences of esophagitis when death occurred. Recently in an autopsy on a patient 76 years old, who died of uremia, following a primary ileostomy for carcinoma of the colon, no esophagitis was found although the tube was in the esophagus for 11 days. Wangenstein (8) stated that in over 5,000 intubations he has never encountered any ill effects from the procedure.

Penner and Bernheim believe that the same cause is responsible for the production of post operative acute esophagitis, gastritis, duodenitis and colitis. This is the mechanism of shock. In their review of the literature they call attention to reports of similar cases by

Billroth, von Eiselsberg, Dieulafoy and others, and dispute the theory of Pringle, Stewart and Thatcher that the lesions are the result of ante-mortem digestion of the esophagus. Briefly the mechanism consists of a series of vascular responses; first arteriolar contraction of varying duration followed by anoxemia, and an associated drop in the gradient of intracapillary pressure, leading to an increase in capillary permeability. Transudation of plasma is followed by the escape of cellular components with punctate hemorrhages into the tissues, and finally necrosis and the formation of pseudomembranes. They have postulated the same theory for the development of 40 cases of severe ulcerative colitis occurring post operatively. In all of their cases extensive operative procedures had been carried on. In our series at least 11 patients who had been operated upon, suffered from what might well be considered shock. The surgical procedures included sub-total gastric resection, repair of perforated duodenal ulcer, relief of intestinal obstructions, multiple perforations of the bowel following a series of pelvic abscesses, appendectomy for acute infection and peritonitis, cholecystectomy and drainage of subphrenic abscess, prostatectomies, and fulguration of carcinoma of the bladder. One of our patients, following a gastric resection, showed not only acute esophagitis, but acute membranous gastritis, duodenitis and colitis. Mosher, as already cited, calls attention to the acuity of the conditions in which esophagitis was found at necropsy. Bartels also comments on the severity of the operative procedures in his report, stating that all of the operations were difficult and extensive, and sometimes the patients were poor risks. While calling attention to this point, here, just as in commenting on intubation and vomiting, many patients die of shock and have not developed acute esophagitis.

Other etiologic factors undoubtedly play a part. Embolism and thrombosis are favored by the presence

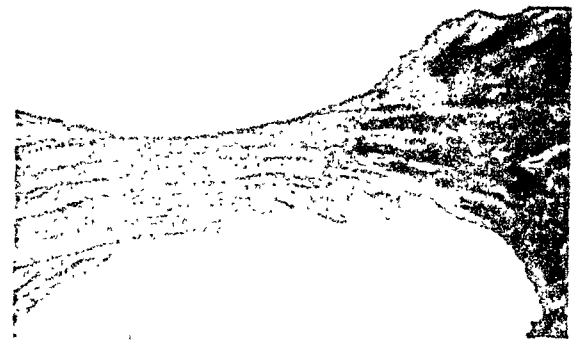


Fig. 2. Acute catarrhal esophagitis. Note the slight exudate on the mucosa.

of large venous channels in the lower end of the esophagus.

The role of the nervous system must also be considered, as Cushing (9) has so forcibly brought out in his report on the formation of perforating lesions in the upper gastro-intestinal tract. Craig and Lipscomb (10) reported a case of cerebellar ataxia, cerebellar tumor with terminal ulceration and hemorrhage of the esophagus. Masten and Bunts (11) cite two cases of esophagitis, one with perforation, in a series

of six cases of esophageal and gastric lesions due to neurogenic causes. One of our cases had syphilitic meningo-encephalitis, another, acromegaly and third acute fulminating encephalitis.

Several writers comment on the frequency of pneumonia as a cause of esophagitis. Invasions of the lymphatics in the lower part of the esophagus and a resultant esophagitis have been described as occurring not only in pneumonia but with many severe intra-abdominal affections as peritonitis, cholecystitis or other septic conditions. However, pneumonia is found so frequently as a terminal event that it becomes difficult to evaluate the role of the pneumonia apart from the other conditions.

The pathologic picture was that of an acute ulcerative esophagitis with formation of pseudomembranes. Grossly the esophagi varied. Most commonly only small islets of whitish mucosa were present, the rest of the mucosa having disappeared. The submucosa in many instances was hemorrhagically discolored, sometimes of a more reddish-brown color. Here and there small ill defined erosions could easily be recognized. Often lesions in the submucosa appeared in the form of streaks which ran parallel to the long axis of the esophagus. In other instances the mucosa was covered by a varying amount of a greyish, rather friable membrane which could be scraped away with ease leaving hemorrhagically discolored surfaces. In the majority of the cases the changes were found in the mid-portion of the esophagus and its lower third. Frequently the changes stopped abruptly at the cardiac end.

The histologic sections showed a variety of changes. In most instances the mucosa was denuded, the lining cells being completely absent. Throughout the mucosa a varying amount of polymorphonuclear leucocytes and lymphocytes could be easily recognized. Often the mucosa was covered by deposits of fibrin in the meshes of which polymorphonuclear leucocytes were found. Occasionally the inflammatory cells extended into the musculature. The blood vessels in the submucosa were markedly dilated throughout and extravasations of red cells were frequently encountered. The periesophageal fat tissue was hardly involved, and only in rare instances a few polymorphonuclear leucocytes were found in these regions.

In contrast to the chronic form of esophagitis, there seems to be no means of diagnosis of the very acute type. None of the patients had any difficulty in swallowing. In fact most of the patients with this affection were receiving parenteral fluids. Vomiting or regurgitation of blood stained fluid, or obtaining such fluid through a tube should arouse the suspicion of its presence. It is just here that the question arises whether vomiting is a symptom of or the cause of the esophagitis. Unfortunately when acute esophagitis is present, the underlying and primary condition is extremely serious.

One would not expect to suggest any form of therapy of consequence in a case of this type. First the condition underlying the disease itself is exceedingly grave, and second it would seem that what would be to the advantage of one would not be of value to another. One would hesitate to pass a Levin tube if esophagitis is suspected. Still if this procedure is absolutely necessary, it would have to be carried out gently,

and once the tube is in place, it should not be removed. There is probably little danger of the indwelling tube increasing the degree of esophagitis or perforating the esophagus.

## CONCLUSIONS

1. All of the cases of acute esophagitis in this series, as well as the reports in the literature, were found at autopsy.

2. For the greater part it followed various operative procedures, particularly on the gastro-intestinal tract, and serious medical conditions, as cardiovascular diseases, and infections.

3. No definite etiologic factor is known. Several contribute. Reports in the literature implicate vomiting, the Levin tube, shock, arteriosclerosis, affections of the brain, severe general and local infections and pneumonia. It is difficult to place the blame anywhere definitely. Possibly many factors are at work.

4. The lesion is a very acute process accompanied by necrosis and desquamation.

5. There are no symptoms to indicate its presence, aside from the suggestion offered by vomiting of blood stained fluid.

6. There is no special form of treatment for this condition.

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My thanks are due to Dr. Otto Saphir, pathologist of the Michael Reese Hospital for his help in the description of the pathology.

## DISCUSSION

DR. J. RUSSELL VERBRYCKE, Jr. (Washington, D. C.): Mr. President, Members of the Association, and Guests: I was particularly interested in the paper of Dr. Bloch because of the fact of having had within the past five months two cases of acute esophagitis of a different type, and of which I can recall having seen only one other during the last thirty years.

This was an acute primary streptococcal esophagitis which corresponded to a certain extent to the ordinary streptococcal pharyngitis, both of which had high temperatures from 102 to 104, dysphagia, leukocytic counts of 15,000 and 16,000, and a rather prompt response to neoprosil.

I think these are rather unusual cases, at least in my experience. It may be that this is more common than I have supposed in other people's experience.

DR. LEON BLOCH (Chicago, Ill.): There is only one additional point I want to make. There are quite a number of reports in the literature of what was taken to be acute esophagitis, but in none of these patients was the condition actually seen by esophagoscopy. The authors

surmised that the patient had esophagitis because of symptoms. The important thing to call attention to is that none of the patients in whom the acute, necrotizing type of esophagitis was found, had any symptoms suggestive of the underlying condition. The patients were too sick to take any nourishment by mouth and were given parenteral fluids.

Slides of various degrees of esophagitis were presented showing large areas of the esophagus denuded of mucous

membrane, and small islets persisting in other views. Other slides revealed pseudomembrane formation along the lower half of the esophagus, or larger hemorrhagic areas. One slide revealed an acute esophagitis superimposed upon a chronic process in a woman of 30, in whom, despite the presence of symptoms of peptic ulcer, an ulcer of the stomach or duodenum was not found on operation. A clinical diagnosis of peptic ulcer of the esophagus was therefore made, which was later substantiated at autopsy.

## The Gastro-Intestinal Manifestations of Shock

By

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and

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ALMOST 75 years ago Billroth (1) noted a single case of melena coming on shortly after an unsuccessful attempt to remove an enormous struma. He attributed the multiple ulcerations, which he found in the duodenum, to a post-operative sepsis although he admitted that there was no evidence of sepsis at autopsy. Since then there have been numerous reports in which focal erosions and ulcerations have been observed in all portions of the gastro-intestinal tract from the lower end of the esophagus to the rectum. These have been analyzed elsewhere (2).

The explanations offered for the origin of such ulcerations are as varied as the type of clinical conditions in which they occurred. As already mentioned, the first explanation was that they were due to sepsis. Von Eiselsberg (3), who also described such lesions in the stomach and duodenum in post-operative fatalities, considered them to be due to retrograde emboli from thromboses in the omentum. In this, he was supported by his students Busse (4) and von Winiwarter (5) who, however, were primarily interested in cases of melena which appeared in patients shortly after operation. Dieulafoy (6) also observed gastric bleeding post-operatively and found gastric ulceration at autopsy. He considered the lesions to be due to a "toxi-infectious" cause, similar to that which caused identical symptoms in cases of pneumonia. Bartels (7) observed 82 cases of esophageal ulceration in a study of 6,000 esophageal specimens from the Mayo Clinic. He considered the lesions to be due to regurgitated gastric juice. Similar lesions have been noted after brain operations and have been attributed to lesions in the interbrain or its various tracts (8). The resemblance of these lesions to those of bacillary dysentery led to stool culture in several cases (9), with uniformly negative results. The anatomical changes, therefore, were considered to be due to putrefactive changes in the stomach and intestines. In the rectum they have been attributed to enematia.

From the clinical side a study of the protocols from the literature as well as of our own shows that the patients in whom these lesions occur are often described as "being poor surgical risks," "debilitated but not necessarily dying," "in collapse," etc. Where

such are available these protocols are almost monotonous in their uniform descriptions of a state of collapse in the patients in whom these lesions occurred (7). In addition, some cases presented hematemesis or melena in the last few days of life. As a rule, however, these patients are described as being distended and having difficulty in passing flatus. They are prostrated, pallid, occasionally somewhat cyanotic. Their pulses are thready, frequently described as "imperceptible," intermittently, for days before death. In our own material the latter findings have at times been associated with distinctly visible and forceful pulsations in the carotid vessels. Our own observations as well as those which we have collected from the literature led us to the conclusion that, despite the wide variety of clinical states in which these lesions have been observed at autopsy, there is one physiological state which they have in common. The clinical descriptions leave no doubt that these patients were in a state of shock which in many instances had lasted for several days before death.

An examination of the anatomical features of these lesions shows that there is a very definite sequence of changes which is characteristic for each localization in the gastro-intestinal tract. Thus, the earliest changes which we have detected in the stomach were found in the interglandular stroma of the mucosa. In the small intestine, colon and esophagus, however, the initial changes were found in the submucosa.

A second feature which is typical of these lesions is their focal nature. The earliest changes, regardless of their primary localization in the mucosa or submucosa, are focal and the larger lesions represent a fusion of multiple focal lesions.

At the onset one sees a striking dilatation of the venules and arterioles which is noted in the mucosa in the case of the stomach but in the submucosa elsewhere in the gastro-intestinal tract. In reconstructing the further course of the process we find these dilated vessels surrounded by a relatively acellular edema fluid. The latter later shows the presence of red blood cells which in the absence of organic lesions of the vessel walls is attributed to diapedesis. At the stage at which these focal hemorrhages are found, similar

tissue changes are found in the other layers of the gut wall.

In the esophagus and small and large intestines the mucosa is eventually involved so that the tips of the villi in the latter become necrotic and slough off leaving a superficial erosion. In the esophagus a small focus of the epithelial lining is involved and on separating off leaves a minute ulceration. These spread by fusion so that one finds a large desquamated area which is covered by a membrane consisting of fibrin, necrotic epithelial cells as well as white blood cells and red blood cells. In the intestine we have seen individual villi showing tip necrosis while the surrounding villi appeared normal or showed other stages in the above process. Here, however, a similar fusion of focal lesions occurs and there is also formed a pseudomembrane.

In the case of the stomach the pathological alterations extend toward the submucosa which may eventually be involved. Here, also, we have observed involvement of the stroma between individual gland tubules. These fuse and extend into the depth of the mucosa so as to form an erosion, the base of which consists of a layer of necrotic mucosal cells enmeshed in fibrin which also contains red blood cells and white blood cells. These erosions may extend through the muscularis mucosa into the submucosa.

Such lesions may spread so as to involve all the layers of the bowel wall and give rise to a reaction on the peritoneal surface.

The basic physiological disturbance occurring in shock consists of a discrepancy between the volume of circulating blood and the capacity of the circulatory system, in which the former is too small to adequately fill the latter to a degree compatible with the needs of the tissues. The response made by the organism to this disturbance, involves a redistribution of the circulating blood so that the flow to the brain, heart and lungs will be maintained to an extent at least compatible with life. This is accomplished by vasoconstriction predominantly involving the vascular bed of the abdominal viscera. In addition, contraction of blood reservoirs occurs so that the liver and spleen discharge their blood reserves into the circulation.

The visceral vasoconstriction may result from neural discharges reaching the viscera through the sympathetic nerve supply, or from the peripheral action of adrenalin discharged from the adrenal medulla. Both mechanisms may act together but it seems that the hormonal is the more powerful and prolonged. In any case we have observed lesions in the gastro-intestinal tract in cases in which, as far as could be ascertained from the clinical history, shock had been present for as short a time as  $\frac{1}{2}$  hour before death. The vasoconstriction, however, is not uniform in distribution as has been shown by Rein and his co-workers (10), by Blalock and Levy (11) as well as by Orahovats (12). The latter has shown that there are marked variations in the visceral vasomotor areas which respond to various stimuli in a given species.

In the ordinary course of events the need for such vasoconstriction is of short duration and its degree not sufficiently marked to lead to tissue changes which are morphologically detectable. However, in the severe cases the shocking stimulus may persist and be of

sufficient intensity to call forth a vasoconstriction which may lead to organic changes in the viscera in which it occurs. In the first instance the vasoconstriction disappears with no residua. In the latter, however, the vasoconstriction disappears as a result of local tissue changes caused by the ischemia which it creates, despite the persistence of the shocking stimulus. The "outlying acidosis due to functional ischemia" (Rous and Drury) (13) has been known for many years to be able to produce vasodilatation. This is in all probability accentuated by the formation of other tissue metabolites such as adenylic acid (Gaddum) (14).

The anoxemia and drop in pressure gradient within the capillaries leads to an increase in permeability of the capillary endothelium. As a result the plasma proteins are no longer retained to the extent to which they normally are, and we thus are able to see the protein containing edema fluid in the tissue spaces as an early morphological change. This loss of plasma protein from the circulating blood further reduces blood volume and thus a vicious circle is set up. In addition the edema serves to impede the transfer of oxygen to the tissues and thus hastens and increases the anoxemia.

The persistence and increase in the capillary permeability leads to eventual diapedesis, a morphological change which we have repeatedly seen. In addition, the blood concentration and the increase in fibrinogen of the blood seen in shock (Cannon) (15) sometimes leads to the formation of capillary thrombi which we observed in our own material and which was reported 20 years ago by Bierende (16), in similar cases. The above changes form the background for the anoxic tissue necrosis which follows, and which results in the appearance of multiple focal lesions corresponding to the vascular areas participating in the compensatory vasoconstriction.

In order to test the validity of the above hypothesis we decided to attempt to reproduce the vasospasm known to occur in shock but to avoid the introduction of uncontrollable factors such as complicated operative procedures. This was accomplished by the administration of adrenalin intraperitoneally in such doses that there would result an average concentration estimated to vary from 0.003 to 0.01 mg./kg./min. for a period of about two hours. This was done using rabbits, guinea pigs, dogs and cats.

A histological study of the resulting lesions showed that we were able to reproduce all the various stages in the development of the lesions which we had observed in our autopsy material. However, we made the interesting observation, that in the dog, the earliest changes in the intestines did not occur in the submucosa as they do in man. In this animal the earliest deviations from the normal are seen in the mucosa just as they are in the stomach of man. This striking difference could only be due to a basic anatomical difference in the blood supply of this animal in comparison with that which occurs in man. Such a difference had been described by Spanner (17) in 1932 when he showed a striking difference in the location of arteriovenous anastomoses in the wall of the intestines of various animal species.

In man, rabbit, rat, mouse and bat (Fig. 1) he described the main arteriole of a villus as passing up the villus without branching until it reaches the tip where it divides into two branches. One of these breaks up into the capillary network which participates in the absorptive functions of the villus. The other branch, which is larger than the capillaries in calibre, passes



Fig. 1. Diagrammatic representation of the mucosal and submucosal circulation as it occurs in man, rabbit, mouse and bat. Modified from Spanner (17). Arteries black; veins white. The arteriovenous short circuit is located near the tip of the villus. The blood is directed through the central vein of the villus simultaneously with the spasm of the other terminal branches of the submucosal arteriole. There are located in the submucosa and are indicated by circles at their point of origin.

directly into the large central vein of the villus and forms an arteriovenous shunt. By direct observation Spanner showed that the blood flow is directed through the capillary bed during digestion while during starvation or in the interdigestive phase the blood flow passes through the arteriovenous shunt into the central vein, and the capillaries are empty. The blood flow through the villi is thus adapted to varying functional needs.

In the case of the dog, cat, pig and horse (Fig. 2) Spanner found the arteriovenous shunt to be located in the submucosa and to differ strikingly in structure from those in man. They arise proximal to the origin of the mucosal vessels from the larger submucosal arterioles and are thus intercalated proximal to the mucosal vessels. They are narrow in calibre at their origin but show a large bulbous dilatation distal to this point. In these animals the flow of blood can thus pass directly into the submucosal veins and in this way avoid flowing through the villar vessels since the

arteriovenous shunt occurs proximal to the site of origin of the latter.

From our observations in man and in the dog (18) we concluded that in addition to the deviation of blood flow through the arteriovenous shunt there must occur a vasospasm which involves the arteriolar vessels which form the other terminal branch of the submucosal arteriole than the arteriovenous anastomotic vessel. This combination of events would, in the dog, lead to a shunting of the blood flow through the submucosa and a constriction of the arteriole to the villus which forms the other terminal branch of the submucosal arteriole. In this way the villi would be the first structures to be subjected to the resulting anoxemia and the pathological changes would take their origin in these structures. In man, however, the same sequence of events, i.e., short circuit of blood flow through the arteriovenous anastomosis associated with vasoconstriction in the other terminal branches of the submucosal arteriole, leads to a deviation of the blood flow through the villi since the arteriovenous anastomosis is located in these structures. The simultaneous



Fig. 2. Diagrammatic representation of the mucosal and submucosal circulation as it occurs in the dog and cat. Modified from Spanner (17). Arteries black; veins white. The arteriovenous anastomosis is located in the submucosa. The other terminal branch of the submucosal arteriole which goes into spasm supplies the villus and is indicated by a circle at its point of origin.

vasoconstriction of the other terminal branches of the submucosal arterioles, which are all located in the submucosa, leads to a submucosal anoxemia which if severe and persistent would result in the tissue changes described above.

In order to test the validity of the above hypotheses we repeated our experiments in cats which possess the



same vascular distribution in the gastro-intestinal tract, as dogs. In addition, the same procedure was repeated in rabbits and guinea pigs in which the blood distribution is identical with that of man. To avoid repetition we may summarize by stating that the pathogenesis of the lesions in the cat is identical with that in the dog, while in the rabbit and guinea pig it is similar to that in man. We feel that this offers additional and important evidence as to the validity of the vasospastic theory of the origin of the intestinal lesions occurring in shock.

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## DISCUSSION

DR. ROBERT ELMAN (St. Louis, Mo.): Mr. President, Ladies and Gentlemen: I was very much interested in the presentation of these findings, which are essentially a correlation between shock and gastro-intestinal lesions.

I am not clear in my own mind, however, whether it isn't possible that the manifestations of shock are not caused by the gastro-intestinal lesions rather than vice versa. Certainly, in other surgical conditions, such an etiological relationship seems clear.

A number of years ago Warren Cole and I observed very severe shock within an hour in experimental animals following ligation of the portal vein. We were able to demonstrate that this shock was due to the loss of blood into the gastro-intestinal tract induced by the portal obstruction. Blalock was able to show that in the experimental animal mere manipulation of the gastro-intestinal tract was followed by so much loss of plasma into the peritoneal cavity, and the wall of the intestine, that surgical shock resulted. More recently Fine has demonstrated in patients suffering from intestinal obstruction with distension, a very definite fall in the plasma volume as measured by direct estimations.

This idea has therapeutic implications. We recently had such an experience in a patient who had a ruptured appendix with general peritonitis, who did very well for a week and then became worse and showed all the clinical manifestations of shock. The red count was high, serum protein was low, and we felt she was suffering from a loss of plasma similar to that which occurs in burns. Replacement therapy, that is to say, plasma transfusions resulted in a miraculous change in the patient's general condition. The child received 10 cc. of plasma per kilo, repeated three times within thirty-six hours and recovered promptly.

These considerations, it seems to me, do raise the question as to which comes first, the chicken or the egg. Certainly it seems to me that in a good many gastro-intestinal lesions there may be a sufficient pouring out of serum from one cause or another to lower the blood volume and in itself produce the manifestations of surgical shock;

if this etiological condition is true, the therapeutic inference is clear—what these patients need is replacement of plasma protein by way of plasma transfusions.

DR. RUSSELL S. BOLES (Philadelphia, Pa.): Mr. President and Members and Guests of the Association: I want to take this opportunity of expressing to Dr. Klemperer and his colleagues my very deep interest in this subject, and appreciation of the work that they have done. I think this is very vital, fundamental, and pioneer work, especially in the bearing it may have on the etiology of peptic ulcer.

For some time I have felt that we must begin the study of ulcer from a broad, fundamental point of view, and I believe this work of Dr. Klemperer's and Dr. Penner's is a very refreshing approach along that line, trying to solve this question by beginning, as it were, at the source.

It gives me particular pleasure to observe that their presentation today exactly confirms, as I see it, the report made here by Dr. Riggs and myself last year, on the role of disturbances of the circulation in the production of ulcer.

I should like to remark at this time that I believe we have evidence to show that his findings have a very logical, practical basis; from a study of sections of the brain, the hypothalamus and its centers, of the vagus nerves, the liver, kidneys, and other viscera in cases of acute gastric ulceration, we believe we can show a very definite correlation, between the lesions in the stomach and certain disturbances in the circulation of the type that Dr. Penner has described, which are primarily brought about by alterations of function or pathological changes in the vegetative nervous mechanism.

The evidence I am referring to will be presented in a paper by Dr. Riggs and myself before the Section on Gastro-Enterology this week.

A study of the serum proteins, blood volume, viscosity, vitamins, etc., are all matters of great importance in the solution of this question of the etiology of ulcer. Dr. Penner remarked on the effect of prolonged adrenal stimulation. This is extremely important. In the literature one will observe scattered reports indicating that adrenal stimulation does not produce acute gastric ulceration. I believe Dr. Klemperer and Dr. Penner will substantiate the statement that such is the case only when short, transient periods of adrenal stimulation are produced. As shown by them, acute ulceration does occur from prolonged periods of adrenal stimulation which they were very careful to produce through their peritoneal injections.

There are a great many other things I should like to say in connection with this subject had I the time. Again I would like to congratulate Dr. Klemperer and Dr. Penner. Thank you very much.

DR. ABRAHAM PENNER (New York City): With regard to Dr. Elman's question as to which comes first, the chick or the egg, these lesions have been observed not only in instances where operations had been performed upon the gastro-intestinal tract. We have cases in our collection with identical lesions which occurred following pulmonary embolization, in which there was no question of an intestinal lesion as a primary factor, and also several cases in which the lesions occurred following severe coronary thromboses, in which again there was no question of primary intestinal involvement. We have also observed the same lesions in fatal cases of diabetic coma. Similarly cases have been reported in the literature following insulin shock therapy for schizophrenia, so it is not primarily a case of loss of fluid into the intestinal wall.

I think it should be emphasized that in talking about shock, and especially in mentioning shock in this connection, that the word itself may be misleading in that what we are essentially discussing is not shock as it is mani-



festated clinically or as a clinical concept. In the pathogenesis of these lesions we are concerned with the compensatory mechanisms which are called forth by any one of the varied stimuli which may create the clinical state of shock, so that if we may be permitted to do so, we should really employ the word homeostasis, which Cannon has employed, and considered this a vasomotor homeostasis, which is reaction on the part of the body to any stimulus which might conceivably put the organism into shock.

DR. PAUL KLEMPERER (New York City): Mr. President and Members of the Association: I just want

to say one word and that is that these investigations of Dr. Penner and Dr. Bernheim have been conceived entirely originally by Dr. Penner and Dr. Bernheim, and my own role in that was only that of a most interested observer who followed the investigations from the very first day, and the only part I can claim is that I have encouraged them to do as much as they could.

I should like to add that Dr. Penner and Dr. Bernheim have extended these investigations to other parts of the body and that, for instance, investigations on the role of shock and after adrenalin on the kidneys are under way and will be reported on in due time.

## The Occurrence of Gastritis as Diagnosed by Gastroscopy in Gastric Neuroses\*

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### INTRODUCTION

CLINICIANS are constantly confronted with the problem of the patient who complains of upper abdominal distress conforming to no recognized symptom-complex, and in whom all studies including the general physical examination, routine laboratory procedures, gastric analyses, and X-rays fail to establish the diagnosis. This type of patient is usually classified as having a functional gastro-intestinal disturbance or a gastric neurosis. With the advent of gastroscopy, it is not surprising that extensive studies should have been made to determine the relationship, if any, between the appearance of the gastric mucosa and the symptomatology of patients of this type. Recent publications (1, 2, 3) have called attention to the frequency with which deviations from the normal have been observed with the gastroscope. The changes described have been generally accepted as indicating an inflammatory process, or chronic gastritis. Chronic gastritis is reported to occur in 35 to 50 per cent of patients (4, 5, 6, 7, 8, 9, 10). Schindler (11), who undoubtedly has performed more gastroscopies than anyone in this country, reports that 41.8% of all patients gastroscopied by him had gastritis. Another observer (3) states that one-half of radiologically negative stomachs have organic lesions demonstrable by gastroscopy.

Inasmuch as the gastroscopic studies made at Duke Hospital do not confirm these generally accepted statements in regard to the frequency of gastritis, it was felt that a critical examination of our data might be worthwhile.

### MATERIAL

This report is based upon an analysis of 543 gastro-

scopies done at Duke Hospital within the past two and one-half years. All the examinations were performed by one observer (J. M. R.). In every case, Elon Clark, head of the Art Department of Duke Medical School, observed the gastroscopic picture and recorded his independent impressions of the color changes present. Colored drawings have been made in 143 cases.

Of this group of 543 gastroscopies there were 240 patients who complained of indefinite upper abdominal distress, and in whom all diagnostic studies were negative. These patients have been grouped arbitrarily under the classification of gastric neurosis, and their findings will now be presented in detail. All patients in this series were residents of North Carolina.

The distribution by age, race and sex is shown in Tables I, II and III. The majority of patients were males, and 60% of them were between 20 and 40 years of age. Because of the usual lack of cooperation and difficulty of the gastroscopic procedure, only a few negroes have been studied.

The gastric mucosa was found to be entirely normal in 151 patients (63%). Hemorrhagic, or pigment spots were observed in 60 patients (25%). These spots are small, sharply circumscribed areas varying from 1-3 mm. in diameter and seem to be beneath the surface of the mucosa. They vary in color from bright red to dark brown or black and the surrounding mucosa appears entirely normal. Frequently, one will observe a bright red halo around a dark spot. These spots have been referred to by Schindler (12) as "localized gastric purpura" and he thinks that they are in some way related to peptic ulcer. Other observers (13) have questioned their significance. In 23 patients (9%) the mucosa seemed thin and the usual folds were absent, and in some of these patients blood vessels were seen. Hypertrophic folds, or a cobblestone mucosa, were seen in four patients and shallow super-

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TABLE I  
Distribution by age, race and sex  
(240 Patients)

AGE		
	No.	Per Cent
10-19	13	5
20-29	62	26
30-39	81	34
40-49	36	15
50-59	33	14
60-69	12	5
70-79	3	1
Total	240	100

TABLE II

RACE		
	No.	Per Cent
White	236	98
Colored	4	2
Total	240	100

TABLE III

SEX		
	No.	Per Cent
Male	151	63
Female	89	37
Total	240	100

ficial erosions in two. Therefore, if Schindler's conception and classification of gastritis is accepted, chronic gastritis occurred in only 12% of this series of patients (Table IV).

There was no characteristic symptomatology and no correlation between the patient's complaints and the gastroscopic picture. This has been pointed out by other investigators (14, 15). However, it has been stated that atrophy of the gastric mucosa (atrophic gastritis) causes characteristic constitutional symptoms (16). As shown in Table V, the symptoms of those patients whose gastric mucosa was normal were not significantly different from those whose mucosa was atrophic, or in whom hemorrhagic or pigment spots were observed. In the 23 patients whose gastric mucosa was atrophic, no characteristic constitutional symptoms were noted. 32 students, who had no digestive complaints, were gastroscopied as normal controls. In five (16%) hemorrhagic, or pigment spots, were observed. The gastric mucosa of the remaining 27 was entirely normal.

The following cases are reported as typical of patients whose gastric mucosa was recorded as (1) normal; (2) atrophic; (3) showing pigment spots.

#### (1) CASE REPORT

E. B. C. (History No. A-11740), a 28 year old white married man entered Duke Hospital November 22, 1938, complaining of gas and indigestion for several years. This

was experienced at any time but especially after meals. In addition to this, there had been a dull burning in the epigastrium usually noted two to three hours after meals and which was occasionally relieved by food and soda. There had been no nausea or vomiting. A Sippy diet had been followed without relief. His diet had been adequate. He denied the use of alcohol but smoked ten to fifteen cigarettes a day.

The general physical examination was negative except for slight epigastric tenderness.

*Laboratory procedures:* Urine negative. Hemoglobin 98%. WBC 4,800. Wassermann negative. Gastric analysis, 85° free HCl. Gastro-intestinal X-ray series negative.

*Gastroscopy:* The mucosa was entirely normal exhibiting the usual orange-red color and normal folds. The pylorus was seen and observed to be normal.

*Impression:* Gastric Neurosis.

#### (2) CASE REPORT

S. W. S. (History No. 82285), a 28 year old white, single mechanic entered Duke Hospital February 17, 1938, complaining of "stomach trouble" of three years duration. This was described as a burning sensation in the mid-epigastrium unrelated to meals and relieved occasionally by food and soda. For the past year and a half he has noted gaseous distention and eructations. He noticed occasionally a slight area of tenderness just below the umbilicus in the midline which was accentuated by nervousness or fatigue. There had been no weight loss. His diet had been adequate. Alcohol and tobacco were used in moderation.

The general physical examination was entirely negative.

*Laboratory procedures:* Urine negative. Hemoglobin 101%. RBC 5,440,000. Wassermann negative. Gastric analysis, 95° free HCl. Gall bladder and gastro-intestinal X-ray series were negative.

*Gastroscopy:* The mucosa was atrophic with few folds. There were no pigment spots or blood vessels. The pylorus was well seen.

*Impression:* Gastric Neurosis.

#### (3) CASE REPORT

E. C. M. (History No. A-1300), a 29 year old white, married merchant entered Duke Hospital May 9, 1939, complaining of "stomach trouble" for the past three years following an attack of "flu." He first complained of gas and fullness in the lower abdomen. This has persisted until present and has been accompanied by belching and the passing of flatus. He has had no actual pain and his appetite has been good. The diet has been adequate and he uses alcohol and tobacco in moderation.

His general physical examination was entirely negative.

*Laboratory procedures:* Urine negative. Hemoglobin 86%. WBC 5,800. Wassermann negative. Proctoscopic

TABLE IV  
Gastroscopic findings  
(240 Patients)

	No.	Per Cent
Normal mucosa	151	63
Hemorrhagic or pigment spots in an otherwise normal mucosa	60	25
Atrophy of mucosa	23	9
(a) Alone	13	
(b) With spots	10	
	23	
Hypertrophic folds or cobblestone mucosa	4	2
Erosions	2	1
	240	100

TABLE V  
*Symptomatology*

	Normal		Spots		Atrophy	
	Number	Per Cent	Number	Per Cent	Number	Per Cent
Gas	42	27	21	35	5	22
Nausea	24	22	10	17	7	30
Vomiting	28	18	8	13	5	22
Ulcer syndrome	26	17	5	8	2	9
Indigestion	25	16	14	23	4	17
Epigastric burning	18	12	9	15	..	..
Vague abdominal pain	18	12	8	13	6	26
Epigastric pain unrelated to meals	15	10	9	15	5	22
Weakness	12	8	3	5	..	..
Distention	10	6	4	7	1	4
Nervousness	10	6	8	13	1	4
Choking	4	3	..	..	..	..
Belching	4	3	..	..	1	4
	151		60		23	

examination negative. Gastric analysis, 59° free HCl. Gastro-intestinal X-ray series negative.

*Gastroscopy:* There were numerous small pigment spots scattered throughout the stomach near pylorus, 1-2 mm. in diameter and deep red to brown in color. These spots were on the crests of the folds and the surrounding mucosa was entirely normal.

*Impression:* Gastric Neurosis.

As will be observed, there are no significant differences in the symptomatology, physical findings or the results of laboratory examinations in these three cases. Yet, in the first the gastric mucosa was entirely normal; in the second, the mucosa was atrophic, and in the third, there were numerous pigment spots.

The incidence by decades of the different gastroscopic findings is shown in Table VI. It will be noted that with advancing years the percentage of normals progressively decreases. However, in the second, seventh and eighth decades there are so few cases that no conclusions can be drawn. Likewise, the percentage of pigment spots is about the same in the third, fourth and fifth decades. The smaller percentage in the remaining decades may be of no significance because so few cases were observed. Atrophy may occur in young

people, but seems to be more prevalent in later life.

The relationship of diet, alcohol, tobacco, anemia and free HCl is shown in Table VII. It will be noted that none of these factors play any significant part in the gastroscopic picture, except in cases of dietary deficiency, in which atrophy of the gastric mucosa is very commonly seen.

DISCUSSION

There is a rapidly growing tendency today to attribute the symptoms of patients, who several years ago would have been classified as having a functional gastro-intestinal disturbance or gastric neurosis, to the presence of a chronic gastritis. In support of this view minor and insignificant changes in the gastric mucosa, as observed by gastroscopy are described and cited as evidence of an inflammatory process. The observation of mucus in excess of what is thought to be normal, the presence of swollen folds, or the absence of folds is thought to be indicative of chronic gastritis. It is significant to note that there has been little effort to determine just what constitutes the normal gastric mucosa, and what deviation in it may occur without giving rise to symptoms. While it is not surprising

TABLE VI  
*Incidence by decades of gastroscopic findings*

	Normal		Pigment Spots		Atrophy		Hypertrophic Folds		Erosions	
	No.	Per Cent†	No.	Per Cent†	No.	Per Cent†	No.	Per Cent†	No.	Per Cent†
10-19	11	84	2	16						
20-29	41	66	15	24	5	8	1	2		
30-39	51	63	24	30	4	5			2	2
40-49	26	56	11	31	4	11	1	2		
50-59	22	67	6	18	5	15				
60-69	5	42	2	17	3	25	2	15		
70-79	1	33			2	67				
Total	151		60		23		4		2	

†Per cent of total for each decade.

that the profession should have become enthusiastic over a simple explanation of an otherwise difficult problem, yet one wonders whether in their enthusiasm certain observers have not attached too much importance to these minor changes and slight deviations from what is thought to be the normal picture.

In the present study, it is noteworthy that the gastric mucosa was described as entirely normal in 63% of the cases, whereas Schindler found the mucosa normal in only 22.2% (9). Atrophy of the gastric mucosa was observed in 9%, which is fairly close to Schindler's figure of 13.6%. However, he found superficial gastritis in 11% and hypertrophic gastritis in 17.2%, whereas in this series evidence of superficial gastritis was observed in 1% and of hypertrophic folds in 2%.

Although it has been mentioned in recent communications (6, 17, 18, 19) one gets the impression that few gastroscopists recognize the effect of inflation on

more important to recognize that the patient's symptoms are not necessarily related to the changes observed in the gastric mucosa.

CONCLUSIONS

- 1. Chronic gastritis, as diagnosed by gastroscopy, is not common in North Carolina.
- 2. The symptoms of most patients usually classified as having gastric neuroses cannot be explained on the basis of a chronic gastritis.
- 3. Hemorrhagic, or pigment spots, are common (25%), but their significance has not been determined.

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TABLE VII

Gastroscopic Findings	Diet		Alcohol		Tobacco		Anemia		Free HCl	
	Adequate		Deficient		Yes		No		Yes	
	No.	%	No.	%	No.	%	No.	%	No.	%
Normal	41	54	14	9	16	11	50	33	33	20
Pigment spots	30	50	4	7	10	17	23	38	17	28
Atrophy	8	35	6	26	1	4	10	43	3	13

the gastroscopic picture. For the past year in this clinic whenever swollen folds were seen the stomach was inflated with air, and in every instance the folds could be obliterated. As suggested by Forssell (20) and later by Crohn (21), it seems likely that the size and general pattern of the folds are to a large extent, if not entirely, due to the tonicity of the muscular coat of the stomach. If the muscularis becomes stretched or loses its tone, a smooth, if not atrophic mucosa results.

Hemorrhagic, or pigment spots, occur with surprising frequency (25%). These are not associated with any definite symptom-complex and apparently are not related to diet, alcohol, tobacco, anemia, or free HCl. Their significance at the present time is little understood. It is conceivable that they may occur in all people from time to time and heal without leaving a trace of their presence; however, in individuals with an ulcer tendency, they may well be the precursors of peptic ulcers (12).

In the present state of our knowledge of gastroscopy it would seem wiser to describe the findings as observed, rather than to conclude that a smooth mucosa means atrophic gastritis, or that swollen folds are indicative of hypertrophic gastritis. But it is even

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# The Effect of Inflation of the Stomach Upon the Gastrosopic Picture\*

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SEVERAL observers (1, 2, 3, 4) have noted that normal folds can be effaced by inflating the stomach with air. Since some degree of inflation is necessary for observation of the stomach the question may well be raised, what effect, if any, has this upon the gastrosopic picture? In an effort to answer this question, the following study was undertaken.

## CLINICAL OBSERVATIONS

In a series of 543 gastroscopies done at Duke Hospital, it was noted that hypertrophic folds, or a cobblestone mucosa, were seen in only 3.9% of the cases (5), whereas Schindler (6) reports that hypertrophic gastritis occurs in 17.2%. This discrepancy was difficult to understand until about a year ago it was noted that large folds would become normal or completely effaced by inflation. Since this observation was made, it has been noted in every case that large, and apparently swollen folds, became normal or flattened merely by inflation with air; that normal folds tended to disappear, and in a few cases blood vessels were seen where an apparently normal mucosa had been observed previously. At the same time other changes in the mucosa were noted. The usual orange red appearance was gradually replaced by a lighter, less red color and after further inflation a grayish yellow, with a tinge of green, or a pale yellowish orange color was observed. When the folds were completely effaced the mucosa became shiny with many high lights.

Figs. 1, 2, 3 show graphically the effects of inflation of the stomach. In this patient, when only enough air had been introduced to render observation possible, large and apparently swollen folds with pigment spots surrounded by a red halo on the crests were seen (Fig. 1). Then with further inflation the folds became smaller and paler (Fig. 2), and with still further inflation the folds practically disappeared, and the mucosa was a pale yellowish orange color (Fig. 3). The position of the instrument was not changed as is shown by the fact that the same pigment spot was present in all three drawings. The epigastrium was not visibly distended, and on questioning later the patient reported that the stomach felt full, as after a heavy meal.

In another patient, the mucosa was apparently normal when the gastroscope was first introduced (Fig. 4). However, after inflation the folds disappeared and a network of blood vessels was visible. The

mucosa became a pale grayish orange yellow color with many high lights (Fig. 5).

To determine the degree of inflation which was required to effect these changes, careful measurements of intra-gastric pressure were made first in dogs and then in man. Similar measurements have been made by Wilson and Irving (7) who found the average intra-gastric pressure in man lying on his left side was 12 cm. of water.

## EXPERIMENTAL WORK IN DOGS

Gastrosopy in the dog is a simple procedure. The instrument is introduced under ether anesthesia, and the stomach can be well seen except for the pylorus due to the marked "fish-hook" in the dog's stomach. The gastric mucosa of the dog presents essentially the same picture as that of man.

Seven dogs were examined to determine the normal. Then it was observed that not only could folds be effaced by inflation, but that blood vessels appeared such as are usually described as occurring only in atrophic gastritis, and at the same time the mucous membrane became pale yellowish orange in color with many high lights sparkling over its surface. This effect could be duplicated at will.

To measure the intra-gastric pressure, a duodenal tube with a balloon at one end and the other connected to a "U" water manometer was used (Fig. 6). The tube was passed into the dog's stomach with the balloon collapsed, and then the balloon was inflated with a constant amount of air. This was accomplished by closing clamp B and raising the column of water in the manometer by air pressure at A. Then with clamp A closed and clamp B open a constant amount of air could be introduced into the balloon. This method and apparatus are similar to that used by Wilson and Irving (7). The gastroscope was then passed and pressure readings taken as the gastrosopic picture changed. Five dogs were examined in this way and the findings are shown in Table I. The normal folds can be effaced at will. The average pressure at which this occurred was 14 cm. of water. The average pressure at which the blood vessels were seen was 20 cm. of water. The gastrosopic picture at this pressure was indistinguishable from that which has been described as being characteristic of atrophic gastritis (8, 9, 10, 11). Colored drawings showing the artist's impression of the gastric mucosa at different degrees of inflation in dog No. 2 are shown in Figs. 7, 8, 9. It will be observed in Fig. 7 that the mucosa near the objective in the upper part of the field is much redder than that in the center. The balloon is seen at the left.

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The pressure at this reading was 6 cm. of water. In Fig. 8, 1½ minutes later, the intra-gastric pressure was 12 cm. of water and it will be observed that all folds are effaced and the color a light yellowish orange. In Fig. 9, 1½ minutes later, the pressure had been raised to 20 cm. of water and branching blood vessels are seen. The color was then a pale yellowish orange with a tint of gray. The position of the instrument remained unchanged during the experiment.

#### EXPERIMENTAL WORK IN MAN

Pressure studies in man were carried out just as were done in dogs. The tube with the balloon at the

end was passed into the stomach and connected with the water manometer. Then the gastroscope was introduced and pressure readings were recorded with each change in the gastroscopic picture. Three patients were studied in this manner (Table II). The patient was instructed to signal when the stomach felt full or uncomfortable and then no more air was introduced. In patient No. A-39278, the intra-gastric pressure was lowered by eructating which permitted several re-studies of the effect of inflation. The folds could be effaced at will, although this was usually accompanied by a subjective sensation of fullness, comparable to

TABLE I  
*Gastroscopic studies in dogs*

No.	Dog	Time Elapsed	Pressure in cm. of H <sub>2</sub> O	Distention of Abdomen	Portion of Stomach Observed	Gastroscopic Picture
1	Male Wt. 12 Kilos	30 sec.	4	Not observed	Anterior wall	Normal folds; good color
		45 sec.	12	Not observed	Anterior wall	All folds effaced; color less red.
		45 sec.	20	Not observed	Anterior wall	Vessels seen; color less red.
		45 sec.	8	Not observed	Anterior wall	Vessels seen but not so clearly.
		8 min.	4 Deflated	Not observed	Anterior wall	Folds present but not as prominent as at beginning.
2	Male Wt. 12 Kilos	1½ min.	6	None	Anterior wall	Normal folds; good color (1).
		1½ min.	12	None	Anterior wall	Folds effaced; less red (2).
		1½ min.	20	Visible	Anterior wall	Vessels clearly seen; M.M. pale (3).
		30 sec.	10	Relaxed (Same)	Anterior wall	No change.
		9 min.	7 Deflated	None (Size)	Anterior wall	As at beginning.
		3¼ min.	8	None	Anterior wall	Folds effaced.
		15 sec.	12	Soft, enlarged	Anterior wall	Vessels again seen.
3	Female Wt. 16.5 Kilos	4 min.	6	None	Posterior wall	Normal folds; orange red M.M.
		4½ min.	12	None	Posterior wall	Folds effaced; color same.
			12	None	Posterior wall	Vessels easily seen; dull red.
4	Male Wt. 17 Kilos	1 min.	4	None	Posterior wall	Normal folds and color.
		2 min.	18	None	Posterior wall	Folds effaced; M.M. pale.
			8	None	Posterior wall	Same picture.
		6½ min.	24	Marked	Posterior wall	Vessels seen; M.M. glistening and pale.
		8½ min.	38	Marked	Anterior wall	Dull red; network of vessels.
5	Male Wt. 14 Kilos	1 min.	8	None	Anterior wall	Normal folds; good color.
		15 sec.	22	None	Anterior wall	Folds effaced; color lighter.
		2¾ min.	30	None	Anterior wall	Vessels well seen.
		2¾ min.	14	Moderate	Anterior wall	Vessels beginning to fade.
		1 min.	22	Moderate	Anterior wall	Vessels re-appeared.
		2 min.	6 Deflated	None	Anterior wall	Folds present; smaller; no vessels.
		2 min.	14	None	Anterior wall	Folds effaced.
		15 sec.	22	None	Anterior wall	Vessels seen.

(1) Fig. 7

(2) Fig. 8

(3) Fig. 9

what one experiences after a large meal. It is noteworthy that in none of these three patients were blood vessels seen, even though the pressures were raised to approximately the same levels which had revealed them in dogs. The average pressure in man at which the folds were effaced was 21 cm. of water. In the first patient reported in Table II, the gastroscopic picture at the beginning of the experiment is shown in Fig. 10. The intra-gastric pressure was recorded at 12 cm. of water. It will be noted that the folds are about twice the size of the tube lying between them and bright red orange in color. Fig. 11 shows the changes which have taken place 30 seconds later with a pressure reading of 14 cm. of water. The folds are now about the same size as the tube and have become lighter and less red in color. Two minutes later, with a pressure of 20 cm. all folds are effaced (Fig. 12), and the mucosa is pale yellowish orange in color with many high lights.

### DISCUSSION

The observations reported in this communication point clearly to the striking effect of inflation of the stomach upon the gastroscopic picture. Folds which seem large, swollen and inflamed when the instrument is first introduced may appear entirely normal after slight inflation, and can usually, but not always, be obliterated completely by further inflation. In certain instances, folds which appear normal will disappear under inflation and a typical picture of "atrophic gas-

tritis" with blood vessels will be seen (Fig. 5). It should be emphasized, however, that the observation of blood vessels in the gastric mucosa of man cannot be produced in every case merely by inflation, nor can all folds be completely obliterated. It has been noted that the folds on the anterior wall and greater curvature are more easily effaced than in other parts of the stomach. In the anesthetized dog, however, it would seem that the gastroscopic picture can be varied at will, ranging from large, apparently swollen folds to small folds or a smooth mucosa, and with blood vessels easily visible. The pressure required to produce this picture in the dog is about that at which normal folds in man are effaced. This difference between the effect of inflation in the dog and in man may be due to the fact that the dog is anesthetized and, therefore, the musculature of the stomach is relaxed and easily stretched by inflation. It has also been pointed out by Kelling (12) that the stomach may become markedly distended during deep anesthesia. On the contrary, the patient usually is under some nervous tension during the procedure, and therefore has an increased muscular tone.

The question may well be raised, are the folds actually smaller, or is the change in the picture due to the distance from the objective of the instrument, and therefore to differences in magnification? This question is difficult to answer. Certainly, when the stomach is inflated the mucosa is presumably much further away

TABLE II  
*Pressure studies in man*

Patient	Time Elapsed	Pressure in cm. of H <sub>2</sub> O	Symptoms	Portion of Stomach Observed	Gastroscopic Picture
White, Male Age 34 No. A-39743		12	None	Anterior wall	Folds twice size of tube and somewhat redder in color (1).
	30 sec.	14	None	Anterior wall	Folds same size as tube and light in color (2).
	1 min.	18	None	Anterior wall	Folds almost effaced.
	1 min.	20	Full and distended	Anterior wall	Mucosa entirely flattened; color orange gray, many high lights, no vessels (3).
White, Male Age 65 No. A-38568		7	None	Anterior wall	Folds normal in size; usual orange red color.
	1 min.	12	None	Anterior wall	Folds gone; color about the same.
	1½ min.	14	Fullness with sense of pressure	Anterior wall	Mucosa flattened and shiny; no vessels.
White, Female Age 22 No. A-32278		16	None	Anterior wall	Normal folds; good color.
	2 min.	24	None	Anterior wall	Folds nearly gone.
	30 sec.	36	Full and uncomfortable	Anterior wall	Folds entirely gone; mucosa smooth and shiny; less red; no vessels.
	30 sec.	Belched			
	2 min.	11	None	Anterior wall	Folds normal.
	15 sec.	22	None	Anterior wall	Folds gone; color less red.
	30 sec.	11	None	Anterior wall	Folds normal.
	15 sec.	17	None	Anterior wall	Folds gone.
	3 min.	9	None	Anterior wall	Folds normal.
	2 min.	19	None	Anterior wall	Folds gone.

(1) Fig. 10  
(2) Fig. 11  
(3) Fig. 12



Fig. 1—Patient  
(History No. A-36554).  
Appearance of the gastric mucosa  
when instrument was first passed and  
only enough air introduced to render  
observation possible.

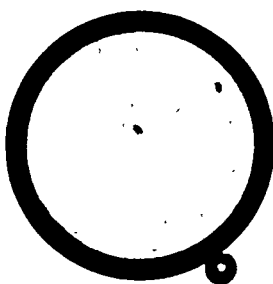


Fig. 2—Same Patient.  
Appearance after further inflation  
showing marked decrease in the size  
of the folds and less red in color.  
Both pigment spots still visible.

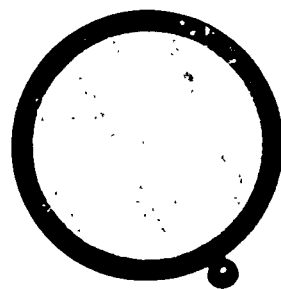


Fig. 3—Same Patient.  
After still further inflation. Folds  
almost completely effaced; much  
paler in color. Only one pigment  
spot seen. Position of instrument  
unchanged in the three drawings.

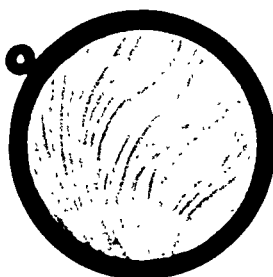


Fig. 4—Patient  
(History No. 38851).  
Appearance of mucosa on introduc-  
tion of the instrument with minimal  
inflation.

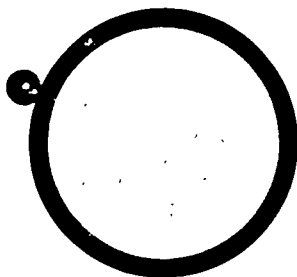


Fig. 5—Same Patient.  
Appearance after further inflation.  
Network of blood vessels visible with  
marked change in color.

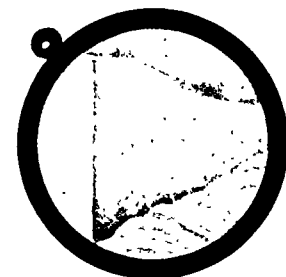


Fig. 7—Dog No. 2.  
Appearance when instrument was  
first introduced. Intra-gastric pres-  
sure—6 cm. of water. The balloon is  
seen at the left.

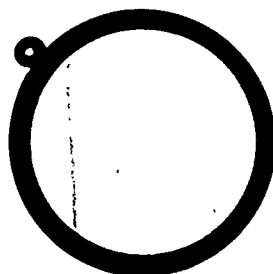


Fig. 8—Same Dog.  
Appearance after further inflation.  
Intra-gastric pressure—12 cm. of  
water. Balloon seen at the left.

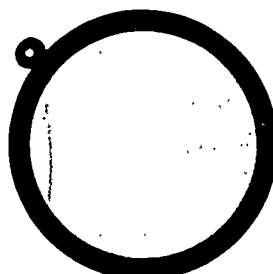


Fig. 9—Same Dog.  
Appearance after still further in-  
flation. Intra-gastric pressure—20  
cm. of water. Balloon still visible.  
Branching blood vessels seen. Posi-  
tion of instrument unchanged in  
the three drawings.

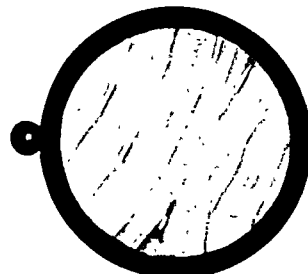


Fig. 10—Patient  
(History No. A-39873).  
Appearance on first introduction of  
the instrument. Intra-gastric pres-  
sure—12 cm. of water. Tube seen  
lying between large, red folds.

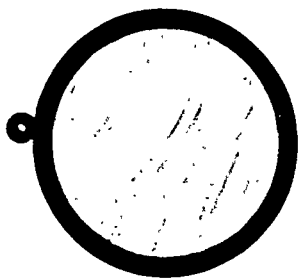


Fig. 11—Same Patient.  
Appearance after further inflation.  
Intra-gastric pressure—14 cm. of  
water. Folds now same size and  
color of tube.

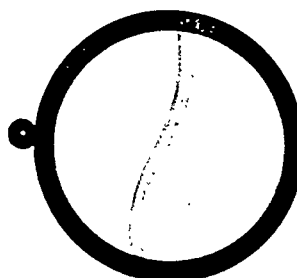


Fig. 12—Same Patient.  
Appearance after still further in-  
flation. Intra-gastric pressure—20  
cm. of water. All folds effaced and  
mucosa much lighter in color than  
tube. Position of instrument un-  
changed in the three drawings.





from the objective, and therefore the image is smaller. However, with the duodenal tube in the stomach it will be seen that the folds actually become smaller by comparison (Figs. 10, 11, 12). It is our belief that with inflation both of these factors should be considered.

While in our experience the effect of inflation of the stomach upon hypertrophic folds cannot be questioned, still we are unwilling to go on record as denying the existence of "hypertrophic gastritis." It may occur, but certainly in North Carolina it is rarely seen. Is it not entirely possible that "hypertrophic gastritis," diagnosed by the presence of large and apparently swollen folds, is merely the result of increased tone of the muscular coat of the stomach, which can be partially overcome by inflation resulting in an apparently normal gastroscopic picture?

Atrophy of the gastric mucosa is another matter. It

is unquestionably true that with very little inflation one frequently sees what has been described as "atrophic gastritis," and inflation could hardly be a factor in such a picture. This is particularly true in the region of the antrum where localized atrophy of the mucosa has been reported so frequently. We are in complete agreement with this observation. However, there is little justification in the present state of our knowledge to call this "atrophic gastritis." It should rather be described as atrophy of the gastric mucosa. It is possible that an apparent atrophy is due to lack of tone of the gastric musculature, and a restoration of tone results in a normal gastroscopic picture.

By referring to Table I, it will be noted that the stomachs of dogs No. 2 and No. 5 were deflated by the introduction of a stomach tube. When re-examined less pressure was required to produce the picture of

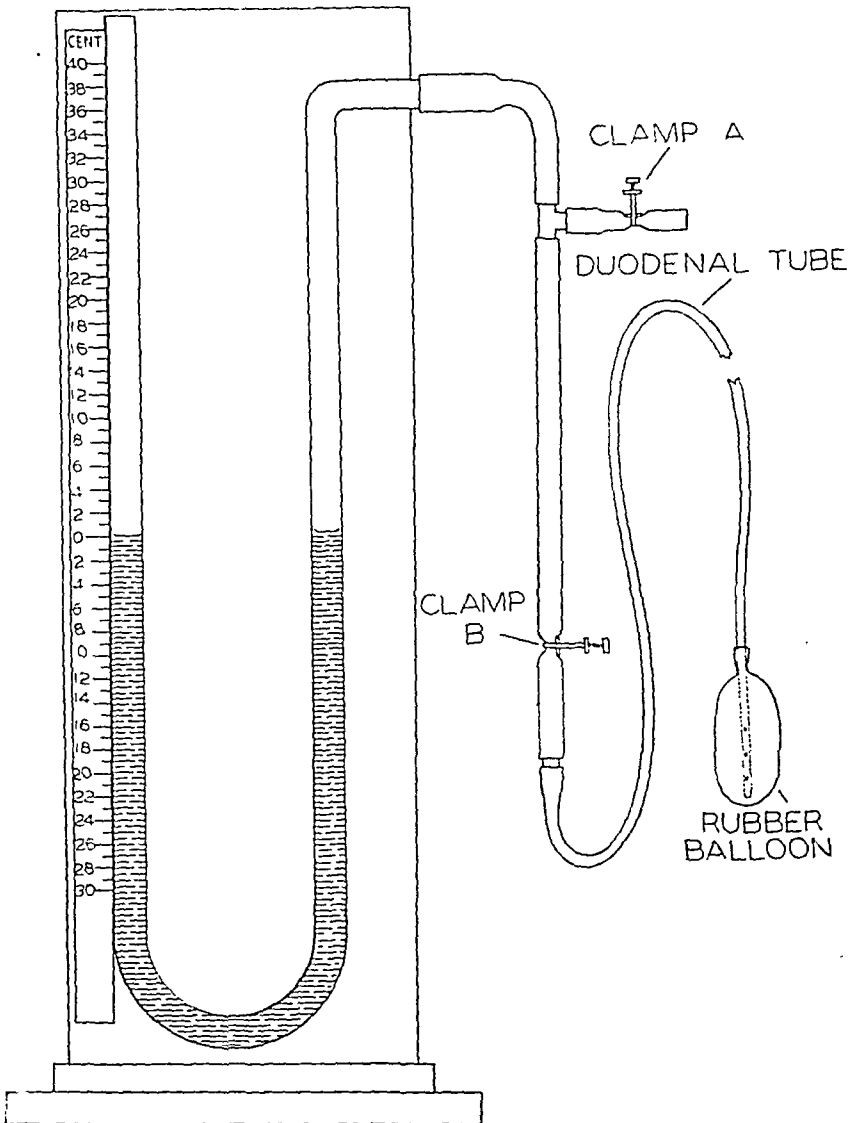


Fig. 6. Diagram of water manometer used to measure intragastric pressure.

blood vessels. Furthermore, a fall in pressure after the original inflation was not necessarily accompanied by a change in the gastroscopic picture. It has been shown by Forssell (13) and recently re-emphasized by Crohn (14) that the character and form of the mucosa are determined by the muscularis. Our observations suggest that the original distention had overcome the tone of the gastric musculature, and that the loss of tonicity was responsible for the apparent atrophy of the gastric mucosa.

When the mucosa is close to the objective, not only do the folds appear large and swollen, but are brilliant reddish orange in color, as will be seen in Fig. 7. The redness varies inversely as the distance from the objective. This is true regardless of the degree of intra-gastric pressure. With increase of intra-gastric pressure the mucosa becomes a grayish yellow with a tint of green or a pale yellowish orange.

### CONCLUSIONS

1. Inflation of the stomach effects marked alterations in the gastroscopic picture.
2. Hypertrophic folds can be effaced by inflation.
3. In the dog, the typical picture of "atrophic gastritis" can be produced at will by inflation.
4. In some instances in man, apparently normal folds will disappear under pressure and blood vessels will be seen.
5. The diagnosis of chronic gastritis by means of the gastroscopic picture should be the subject of further critical studies.

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### DISCUSSION

DR. CHESTER M. JONES (Boston, Mass.): It seems to me that Dr. Ruffin's paper is a very timely one. The time has come when gastroscopy is being freely performed, and the interpretation of gastroscopic findings has been associated with a certain amount of loose thinking and writing, particularly about gastritis. There is still a lack of adequate observations on the normal aspects and variations of the stomach in different conditions and different decades of life. Dr. Ruffin's observations on changes in the appearance of the stomach, with variations in intragastric pressure, are of real importance and justify an honest skepticism of the diagnosis of "atrophic gastritis." There is no doubt that on many occasions this term is a misnomer and that "gastric atrophy" is a much more suitable term,

particularly because of its therapeutic implications. Such studies are very definitely needed.

DR. BURRILL B. CROHN (New York, N. Y.): Mr. President, Ladies and Gentlemen: I, too, feel that this is a very timely paper in so far as it may give us a much more scientific viewpoint as to what actually is the correlation between the changes as seen with the gastroscopy and the clinical symptoms associated with such changes.

At our hospital we gastroscopize cases before operation. The cases were operated upon as soon after gastroscopy as was convenient for the surgeon and the patient. We attempted to make an anatomical correlation between what was seen in the gastroscopy and what was seen with the microscope in resected mucosa, and we found a great deal of discrepancy anatomically between what was called gastritis with the gastroscopy and by the histopathologists. There were wide discrepancies in most of the cases. In a small percentage of the cases there was close association; where the gastroscopist said it was atrophic, and again in a small percentage where it was hypertrophic, one could say there were changes that corresponded. But there was a large field, an overwhelming majority of cases in which you could not find any histopathological basis for the diagnosis of gastritis, nor in the secretory study could we find correlation between secretory changes and gastritis. I think it is conceded by practically all observers that there are no secretory changes characteristic of gastritis; nor could we clinically draw up any syndrome that would correspond with the gastroscopic observations.

I don't think there is any clinical picture that would fit "superficial gastritis," "hypertrophic gastritis"—except in the late stages with so-called atrophic gastritis. The one thing I am able to concede is atrophic gastritis involving the antrum, the same type which was originally suggested by Dr. Eusterman some years ago. That simulates carcinomatous ulcer and leads to many mistakes in diagnosis, and leads to unnecessary resections of the stomach.

DR. GEORGE B. EUSTERMAN (Rochester, Minn.): In view of what has just been said, granting the author's observations are ultimately confirmed, this is another argument for taking a conservative attitude towards the claims of the gastroscopist, who at times may be carried away with his own enthusiasm. I say this because the impression is gained that the experienced gastroscopist can differentiate a small or early carcinomatous ulcer from a benign one with confidence. From repeated personal experience I sincerely doubt this. As a matter of fact, I have seen large benign ulcers unequivocally diagnosed gastric carcinoma by the leading exponents of the gastroscopic art. I am convinced that in many instances the actual differentiation depends on the results of histologic examination.

Reverting to the gastroscopic diagnosis of atrophic gastritis, I occasionally am perplexed at such diagnosis in the absence of other laboratory or clinical evidence of the disease. It is to be hoped that Doctor Ruffin's observations are correct and that such erroneous diagnosis can be avoided in the future. Before we come to any definite conclusions it seems feasible, if it has not already been done, to make observations on the influence of the variations in intragastric pressure in bona fide cases of hypertrophic gastritis. The latter is an acknowledged entity and, in my judgment, a condition most closely and most frequently simulating chronic gastro-duodenal ulcer.

DR. RUDOLF SCHINDLER (Chicago, Ill.): I believe that Dr. Jones is quite right. It is not sufficient to buy a gastroscopist and then try to diagnose gastritis. The foundation of our gastroscopic diagnosis of chronic gastritis was and still is the gastroscopic examination of many healthy adults of all age groups. Changes not found in a

great series of such healthy adults, but demonstrable in patients suffering from abdominal distress, were called pathological. There are two methods at the disposition of the gastroscopist for finding out what is normal and what is pathological, namely: First, to examine a large series of healthy people gastroscopically; or, if he does not have the occasion to do this himself, then to learn the interpretation of the gastroscopic picture with somebody who has had this opportunity.

Now granted that Dr. Ruffin has studied the mucosa of many healthy people—and evidently he has—why is it that in North Carolina those changes were not seen which have been seen before by all gastroscopists in Germany, England, Argentine, and in this country in about the same percentage since 1922. It certainly is an interesting problem, especially because Dr. Ruffin found so frequently isolated pigment spots and hemorrhages which he saw about four times more frequently than they were seen in other regions and countries.

The explanations Dr. Ruffin himself offers to account for the frequent diagnosis of gastritis everywhere else are not valid. Every gastroscopist knows that many folds disappear when air is introduced into the stomach, and time and again it has been emphasized that the thickness of folds cannot be used at all for the gastroscopic diagnosis of hypertrophic gastritis. The gastroscopic signs of hypertrophic gastritis, as described before, are as follows:

"The first sign of beginning hypertrophy is the velvety appearance of the mucous membrane. It appears as slightly swollen, dull, loose, and sponge-like. The highlights are diminished or completely absent . . . The changes . . . appear at first in the valleys between the folds . . . Small, dark creases run through the dull, swollen mucosa. The formation of granular nodules, larger nodules, and big nodules can usually be observed . . . When the mucosal folds are affected they become irregular and are subdivided by perpendicular creases . . . In the very late stages there may be tiny, new folds, exceedingly stiff and short, which cannot be flattened out and hence which never disappear."

All these changes have not been mentioned by Dr. Ruffin, and he did not mention the characteristic gastroscopic signs of chronic superficial gastritis either.

His attempt to explain the frequency of apparently atrophic changes by the finding of similar pictures in the dog's stomach are likewise not valid. We all know since Helsley of San Francisco examined his own dog in 1923 with a rigid gastroscope that the stomach of a healthy dog looks entirely different from that of a healthy human stomach. The dog's stomach usually presents bluish blood vessels, seen as parallel lines especially in the upper anterior wall and the greater curvature where the mucosa looks frequently rather grayish. The gastroscopic appearance of the dog's stomach has been described in my book on pages 84-85.

I, myself, want to offer another explanation for Dr. Ruffin's failure to see the often described and observed gastroscopic signs of chronic gastritis. Against my will a gastroscope was produced in Germany which had a so-called wide angle of vision, an angle of vision of 85 degrees. In order to get an easier orientation the magnification was sacrificed. This was done after I had left Germany. I have always protested against this instrument and have insisted that in this country only 50 degree instruments should be sold (see *Lancet*, 234:1361, June 11, 1938). Only the 50 degree instrument had a magnification which could be compared with the optical effect of the former rigid gastroscopes, and many fine changes simply cannot be seen with the wide-angled instrument.

In the new American gastroscope we have reduced the angle of vision still more and the magnification is now as satisfactory as in the former rigid instrument. May I therefore ask Dr. Ruffin what angle of vision he has used? I believe that with an 85 degree angle many people are unable to make finer observations.

DR. JAMES L. BORLAND (Jacksonville, Fla.): I wish to point out in connection with atrophy as seen in the stomach, that we see about the same percentage of similar changes, both atrophy and hypertrophy, in the rectum. There is no question that true atrophy of the gastric mucosa occurs. It can be seen at operation and verified pathologically.

I should like to ask Dr. Ruffin if he has checked any of his gastroscopy cases with proctoscopy.

DR. LEON SCHIFF (Cincinnati, Ohio): I should like to ask Dr. Ruffin just how he diagnoses atrophy of the gastric mucous membrane, in the light of what he has said. I should also like to ask him if he has made any observations on the relation of the number of bulbuls of air which one introduces into the stomach at the time of gastroscopy to the changes in intra-gastric pressure. For example, how much difference in pressure results from the introduction of two or three bulbuls of air?

DR. H. NECHELES (Chicago, Ill.): I have done a number of gastroscopies on dogs and on men and want to support what Dr. Schindler has said. The diagnosis of gastritis, especially of hypertrophic gastritis cannot be made on the evidence of the size of the folds only. A number of clinical symptoms as well as adherent mucus, color of the mucosa, pigment spots, and so forth help making this diagnosis.

We have been puzzled a number of times by the difference between what we see on the X-ray picture and our observations during gastroscopy. The X-ray picture frequently shows a hypertrophic gastritis, which cannot be seen with the gastroscope; and conversely the gastroscopist sees a hypertrophic gastritis which is not present in the X-ray picture.

We have seen a number of these roentgenologically hypertrophic gastritides disappear after a dose of atropine, and believe they are due to contractions of the muscularis mucosae. We believe that the roentgenological diagnosis of hypertrophic gastritis can be made only after administration of atropine and that the gastroscopic diagnosis does not have to be based solely on the presence of large folds but on all other evidences of inflammation as well.

DR. JULIAN RUFFIN (Durham, N. C.): I realized fully that I was treading upon thin ice and sacred soil in this discussion, but was not deliberately offending anyone. I merely pointed out that one should be careful in drawing conclusions from the gastroscopic picture unless one takes into consideration the factors that I have mentioned.

There is hardly time to answer all the questions which have been raised. So far as atrophy of the gastric mucosa is concerned, we are absolutely certain that this does occur. However, it should not be called atrophic gastritis, but rather atrophy of the gastric mucosa, as it is probably a degenerative process associated with a deficiency state.

In regard to hypertrophic gastritis, we rarely see it. We have seen a few cases with a cobblestone appearance, as has been described, but, unfortunately, we have not seen any of the cobblestone mucosae since we have been studying the effect of inflation. I think Dr. Eusterman is correct in saying that in all probability the hypertrophic gastritis with the cobblestone appearance will not subside under inflation. All I am pointing out is that large, swollen folds

should not be construed as evidence of hypertrophic gastritis.

I do not agree with Dr. Schindler about the dogs. The gastric mucosa of our dogs was very much the same as that of man.

Pigment spots are frequently observed. Their true significance is poorly understood. They may be related in some way to ulcer, but that has yet to be proven.

As to the relationship between gastroscopic and proctoscopic findings, we have studied that frequently and have found no correlation whatever.

It has been asked how many bulbs full of air are required to produce this effect which I have described. This question I cannot answer. However, one cannot measure intra-gastric pressure in that way, as the patient may

eructate or after a period of time the stomach, itself, may relax and, therefore, lower the pressure. The only method of measuring intragastric pressure is an apparatus such as we have used in this experiment.

The X-ray evidence of hypertrophic folds disappearing after atropine is in line with what I have said. The X-ray diagnosis of hypertrophic gastritis probably represents nothing but the contraction of the gastric musculature which throws the mucosa into folds. This subsides when the patient relaxes or is given atropine.

I wish to go on record as saying that gastroscopic examinations are extremely important. They are indeed fascinating, but so far as chronic gastritis is concerned it seems to me that we have gone off on a wide tangent and would do wisely to pull in our sails and start again.

## Gastritis Simulating Peptic Ulcer\*

By

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and

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**M**ANY physicians still hesitate to accept gastritis as a legitimate member of the clinical group of diseases of the stomach. Observations by a number of competent workers correlating symptoms and gastroscopically demonstrable appearance of tissue are indicating the importance and formidableness of gastritis as a symptom-producing entity. Furthermore, some definite impressions regarding the character of the symptoms which gastritis may produce are being formulated.

Moynihan and his school have made the syndrome which spells peptic ulcer so well known that any complex of symptoms suggesting this disease, if such a lesion cannot be demonstrated by roentgenologic examination or exploration, is likely to be classified and often mistreated as a "functional stomach." Further experience with the gastroscope, no doubt will relegate to the limbo of diagnostic subterfuge many terms, such as "Hale-White hemorrhages," "gastrotoxic hemorrhages" and "pseudo-ulcer."

From a review of data available to us for study we have been unable to discover a consistently recurring syndrome for certain types of gastritis. For instance we cannot say that hypertrophic gastritis will regularly cause a certain group of symptoms. Indeed, it may not give rise to any complaints at all. Conversely, however, a syndrome definitely suggestive of peptic, or more particularly gastric, ulcer which includes in many instances the complication of hemorrhage is quite capable of being produced by gastritis. When bleeding is present in these cases, it usually is found to be associated with the superficial dissolution of tissue. Furthermore the development of such a syndrome in the presence of gastritis in a stomach in which the secretory rates are adequate should not be

unexpected. We see no reason to deny to gastritis the same pain producing mechanisms and pathways which are utilized by ulcer in indicating its presence.

### MATERIAL STUDIED AND RESULTS

This discussion results from a review of sixty cases of gastritis, most of which were under our personal observation in the hospital. In many instances it was possible to make parallel follow-up observations on the clinical and gastroscopic condition. Usually the gastroscopically demonstrable improvement, disappearance or reappearance of the intragastric lesion was mirrored in a corresponding mutation in the pattern of the clinical picture.

Cases were accepted for inclusion in this series only if we were convinced that the symptoms which clinically suggested the presence of peptic ulcer were caused by gastritis as demonstrated at surgical exploration or by the gastroscope. In many instances roentgenographic investigations of the gall bladder (Graham-Cole method) were undertaken but results were always negative. No case of gastric anacidity was included. The great majority (75 per cent) of these patients were of a highly nervous, persistent, intensive type, similar in fact to the individuals who are likely to have duodenal ulcer. One of every two patients included in this series was an inveterate tobacco smoker; those who smoked cigarettes were most numerous. Fifty per cent of the patients used alcohol and about a third of these drank immoderately.

It is not within the scope of this paper to attempt a classification of the various types of gastritis and discuss the symptoms caused by each group. In 84 per cent of the cases included in this series chronic erosive or hypertrophic types of lesions were considered to be present; in 40 per cent of these there was evidence of mucosal dissolution. The remaining 16 per cent of the cases in the series were classified as instances of the

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acute catarrhal types of gastritis from the gastric evidence.

A composite picture of the symptoms presented by these patients would cause the presence of a peptic ulcer to be suspected. As in cases of peptic ulcer symptoms were often intermittent. In twenty-three cases symptoms were intermittent at first but later distress occurred almost daily. Twenty-one patients had always had intermittency of bouts but twelve had had distress practically every day since the onset. Four had had attention called to the gastric disorder by symptoms other than distress. The duration of symptoms varied from two weeks to forty years; the average was about eight years.

There was a fairly consistent recurrence of distress at certain definite periods following the meal. In some instances there was epigastric discomfort, a feeling of fullness, sometimes with slight nausea, shortly following the meal. Often distress occurred immediately on eating or a few minutes afterward, especially when coarse, fibrous, fatty or irritating foods had been ingested. This type of distress was most likely to be described as a gassy, filled-up sensation of pressure in the epigastrium with associated bloating, belching and regurgitation. More often, a burning type of distress developed with or without this preliminary disturbance, but with a distinct interval of postprandial comfort. This distress was spoken of as sourness, hunger distress, rawness, heartburn, or just burning pain and was frequently severe. It was often situated high in the epigastrium, was frequently substernal, and at times was in the left side of the epigastrium. The interval of comfort preceding such distress varied from fifteen minutes to three hours, and the type of distress suggested a chemical factor. This symptom caused more than 57 per cent of these patients to wake up at night, usually between 12 m. and 2 a. m. Some of the patients complained of distress which came on before their morning meal. This was especially likely to happen if they smoked a cigarette or two before breakfast. In many instances the pain was very severe. At times it was colicky. One of the most important diagnostic features in these cases was the location of the distress of which these patients complained. In 95 per cent of instances this was indicated as being high in the epigastrium, infrasternal or substernal, often slightly to the left of the midline. In more than 60 per cent of instances the distress seemed to extend upward, under, or along the sternum, or into the throat. Less frequently there was projection of distress to the left side of the thorax or back or even to the shoulder and left arm. This occurred usually during periods when the pain was at maximal intensity.

The ingestion of bland food usually brought relief. An alkali helped, particularly if it caused belching. There was sometimes an atypical response to the use of the stronger alkalis. These might produce complete relief of symptoms for a time, only to be superseded by no relief or even an aggravation of distress following their use.

Systemic manifestations were not marked as a rule. Occasionally, there was anorexia; loss of weight was not marked and weakness was not unusual. In rare cases there was a complaint of dizziness. Many of

these patients complained of vomiting. More often this was actually regurgitation of sour material at the height of the distress.

In 33 per cent of the cases included in this series hematemesis or melena were present. Increased gastric secretory rates were noted in 35 per cent. The average for the group was 56 (Töpfer's method) for total acid and 44 for free hydrochloric acid. Blood tinged gastric contents were observed frequently. Many of these patients commented that the pressure of their clothes hurt the upper part of their abdomens. Epigastric tenderness was usually demonstrable.

Roentgenologic investigations failed to show the presence of peptic ulcer in any of these cases. In many instances two and three investigations were made without demonstrating any ulceration. In 40 per cent of these cases roentgenographic investigation of the gall bladder (Graham-Cole method) was made, always with negative results. In 21 per cent roentgenologic investigation revealed the presence of mucosal irregularities suggested by the roentgenologists as being evidence of gastritis. It is not within the scope of this paper to indicate the method and the results of the treatment of gastritis. Further observations are necessary on the results of treatment, which have been rather encouraging up to the present.

#### SUMMARY AND CONCLUSIONS

Our experience with sixty cases of definitely demonstrable gastritis, usually of the hypertrophic or granular type, scrupulously investigated to rule out all other possible organic or reflex causes for indigestion has led us, after prolonged skepticism, to these convictions:

1. Gastritis should be accepted as a legitimate member of the family of stomach diseases. The task of correlating more accurately the visual, clinical and pathologic findings in such cases however, still remains.

2. The patient who does not give roentgenologic evidence of disease in the upper part of the gastrointestinal tract, but who has symptoms referable to the epigastrium or left hypochondrium, which recur at fairly definite intervals following meals, often recur at night and are relieved by food or soda, even though these symptoms lack the clock-like precision of many peptic ulcers, should be considered to have gastritis, be given treatment for gastritis, and whenever possible gastroscopic examination should be made.

#### DISCUSSION

DR. HENRY A. RAFSKY (New York City): I would like to present two slides to show, how in two different types of cases, the clinical syndrome, which was due to a hypertrophic gastritis, definitely simulated a peptic ulcer.

(Slide) This patient, a 37 year old male, was operated upon for a large duodenal ulcer three years ago. A gastroenterostomy was performed. The patient remained well for about nine months. Since that time he has had periodic recurrences of the ulcer symptoms such as abdominal pain, nausea and vomiting. In addition the patient had three massive hemorrhages during this interval. After the last attack of bleeding he was re-admitted to our service at the Lenox Hill Hospital. All that the X-ray examination showed, at this time, was the large rugae which can be readily seen in the film. I gastroscopied the patient and at the site of the enlarged rugae evidence of a definite hypertrophic gastritis was visualized. No ulcer could be

seen. The patient was again operated upon. At this time no evidence of the previous ulcer could be found, but a thickened indurated area was palpated at the site of the hypertrophic gastritis. This area of hypertrophic gastritis was resected and was reported by the pathologist as "chronic gastritis." It is about fourteen months since this operation was performed and the patient has been well ever since.

(Slide) The next case is a different type of case. This patient was operated upon about ten years ago for what was regarded as an inoperable carcinoma of the pancreas. A cholecystogastrostomy was done to relieve the jaundice. The patient came back two years ago complaining of typical ulcer symptoms such as periodic attacks of pain two hours after eating and relieved by food. The X-ray, as you can see in the slide, showed a good functioning cholecystogastrostomy. No X-ray evidence of ulcer could be seen. When I gastroscopied this patient I found an area of typical hypertrophic gastritis about one inch in diameter just where the bile kept emptying into the stomach. Small deposits of bile could be seen in various folds between the folds. This area of hypertrophic gastritis was confined to the region around this part of the stoma where you see the barium tract. On the basis of this finding, we treated the patient on an ulcer régime and ulcer diet. During the past two years he remained symptom free unless he went off his diet, at which time he experienced a recurrence of his ulcer symptoms.

I would like to show this third slide to illustrate the secretory response in this individual. Notwithstanding the fact that bile keeps pouring into the stomach all the time, you see a typical hyperchlorhydria curve, which is very frequently encountered in peptic ulcer.

DR. ASHER WINKELSTEIN (New York, N. Y.): The method used by Schindler in studying gastritis was to gastroscopie a large number of patients, and, finding a normal appearance or a superficial, atrophic, or hypertrophic gastritis, go back to the clinical symptomatology and attempt to correlate it with the gastroscopic picture. This morning we have seen a tendency, which I think is a very good one, viz., to select very carefully certain clinical groups, gastroscopie them, and then attempt a correlation.

In agreement with Dr. Rivers, I wish to state that we have had at our hospital recently a similar experience. We selected fifteen cases with typical ulcer symptoms, hyperchlorhydria, and negative X-ray findings for gastroscopy. Seven showed gastritis, four hypertrophic and three superficial, and the other eight were normal. We may conclude that about half of the cases with typical ulcer syndrome with negative X-ray findings are functional cases, and the other half are cases of gastritis. Whether the functional cases go into gastritis is conjectural.

We then took fourteen patients with true achlorhydria, determined by the fact that test meals plus histamine and

neutral red showed no secretion of acid or neutral red. Nine of these showed an atrophic gastritis; four were a mixture of atrophic and hypertrophic gastritis.

It therefore seems possible to correlate certain definite clinical pictures with gastroscopic findings.

DR. DAVID H. ROSENBERG (Chicago, Ill.): Mr. President, Members and Guests: I have had the privilege of observing several patients who clinically manifested the peptic ulcer syndrome but in whom the roentgenographic and fluoroscopic findings were entirely negative. Some of these patients had been observed in various clinics, both in this country and abroad, and their symptoms were regarded by some physicians as functional, and by others as organic in nature, that is, due to peptic ulcer. Gastroscopic examinations, however, repeatedly showed chronic hypertrophic gastritis.

I should like to raise the question, Dr. Rivers, whether in some of these patients we may be dealing with an associated duodenitis (with or without superficial ulceration) which may be responsible for the clinical symptoms. One knows full well that in many patients with ulcer symptoms who roentgenographically reveal a negative stomach and duodenum, a superficial ulcer may be found in the duodenum at operation.

I should further like to ask Dr. Rivers his method of therapy in these cases. In my own experience I have found that the usual ulcer régime was all that was necessary.

DR. ANDREW B. RIVERS (Stochester, Minn.): I think that duodenitis is quite capable of presenting symptoms which are similar to those caused by gastritis. It is unfortunate that we cannot explore the duodenum as we do the stomach by means of the gastroscope. This would aid in diagnosing more cases of duodenitis. I am sure, however, that both gastritis and duodenitis are capable of producing symptoms similar to those caused by duodenal ulcer.

Regarding the treatment for gastritis: The time allotted for discussion is too brief to say much about this. I agree with Dr. Rosenberg that the type of therapy to be employed is much like that which is effective in treating ulcer. Each case has to be studied individually and suitable treatment employed. Bland diets, antacids, and anti-spasmodics are important.

Then, too, the use of vitamins in concentrated form is useful therapy. Occasionally, we use gastric lavage of weak silver solutions, metaphen, hydrogen peroxide, or salt solution.

Curtalement of the use of tobacco or alcohol and improvement of the general health are important in the care of this disease.

## Spontaneous Variations in Gastric Secretion in Response to Histamine Stimulation\*

By

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and

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**G**ASTRIC secretion in a given stomach and in response to a given stimulus is quite constant in both dog and man, although there are great variations from individual to individual. In Pavlov pouch dogs, for instance, some animals are known as "good" and others as "poor secretors" of gastric juice. Satisfactory explanations of these differences in the secretory ability or excitability of the gastric mucosa are not at hand. The response, however, of the same animal to repeated identical stimuli is usually quite constant. Histamine has been found to be the most potent and most satisfactory excitant of gastric secretion in the Pavlov pouch dog and in man. Under carefully controlled conditions, tests carried out on the same individual on the same or on successive days have been found to "give results with a variation of not more than 5 to 10 per cent" (1, 2).

The fact that "free acid" is not infrequently found "after histamine" in individuals in whom an Ewald or fractional gastric analysis had disclosed anacidity has been accepted as evidence of the superiority of the histamine test and has led to the conclusion that "histamine-proved anacidity" is "complete" anacidity—"complete" in the sense that it betokens the inability of the stomach to secrete gastric juice with a hydrogen ion concentration of a pH less than 3.5. However, Comfort and Osterberg noted that "histamine failed to cause a secretion of free acid in one case in which the Ewald meal did cause such secretion; it produced secretion of free hydrochloric acid of a concentration less than that evoked by the Ewald meal in two other cases, and it produced concentration only equal to or within 10 points of that evoked by the Ewald stimulus in 14 cases" (3). Henning (4) and Gaither (5) made similar observations. In clinical studies such as these, there are numerous opportunities for technical error and hence it is difficult to draw definite conclusions. The tip of the tube may remain in the esophagus throughout the test or it may pass at once through the stomach into the duodenum. The swallowing of saliva, the regurgitation of duodenal content into the stomach, or the use of an inactive solution of histamine may likewise invalidate the test. Consequently, it is clear that care must be exercised in placing reliance upon even the histamine test although, as has been pointed out, the results are, as a rule, surprisingly constant.

Schiff (6) described a most remarkable case in which transient histamine achlorhydria was noted. The patient, a male 49 years of age without definite

gastric disease, received 799 subcutaneous injections of histamine (0.5 mg. each) and had 433 aspirations of the stomach over a period of four and one-half years. There occurred one phase of complete histamine anacidity as evidenced by three tests at approximately monthly intervals. Following this the free acidity gradually returned, the peak of the curve rising in nine months from a maximum of 14 to a maximum of 64. A year and a half later there occurred a second similar phase of almost complete histamine achlorhydria of approximately five or six weeks duration. There seems to us to be no reason to question the validity of these observations although the explanation of the phenomenon is not apparent.

In the past ten years we have used the fractional histamine test almost routinely and for reasons not germane to this discussion have seen fit to repeat it frequently in certain cases. In general, the results have been fairly constant and uniform. As illustrated in Chart 1, the maximum free acidity as measured in clinical units and the maximum hydrogen ion concentration as measured by the Beckman pH meter in various histamine tests performed during the course of a month in a patient (Case 1, Unit 217214) with gastric ulcer varied somewhat but not greatly. The maximum ten minute volumes showed much greater variations.

We have observed numerous instances in which the results of isolated analyses have been in complete disagreement with the secretory response known to be rather characteristic of the particular stomach. Most of these instances have seemed due obviously to the technical errors previously mentioned, but a few of them have not. These cases appear worth noting in order to emphasize the fact that significant spontaneous variations in the response of a given stomach to a standard stimulus of histamine do occur.

The first case to be cited (Unit 221570)\* is a male 48 years of age who entered the hospital June 7, 1939, after ten years of epigastric distress and one month after the passage of tarry stools. Nausea, vomiting, and epigastric pain were present. A gastric ulcer was demonstrated gastroscopically and roentgenologically, and on July 5 a subtotal gastrectomy, performed by Dr. Phemister, disclosed two small healing gastric ulcers. The first four histamine tests all failed to dis-

\*From the Department of Medicine, The University of Chicago.  
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\*This case and those shown in Charts 3 and 5 were mentioned by Palmer, Walter Lincoln and Nutter, Paul B.: Peptic Ulcer and Achlorhydria. Arch. Int. Med., 65:492, 1940, in the addendum and as cases 2 and 3 respectively. Further details of the case shown in Chart 4 may be found in Palmer, Walter Lincoln; Schindler, Rudolf, and Templeton, Frederic E.: The Development and Healing of Gastric Ulcer—A Clinical, Gastroscopic and Roentgenologic Study. Am. J. Dig. Dis., 5:501, 1938.



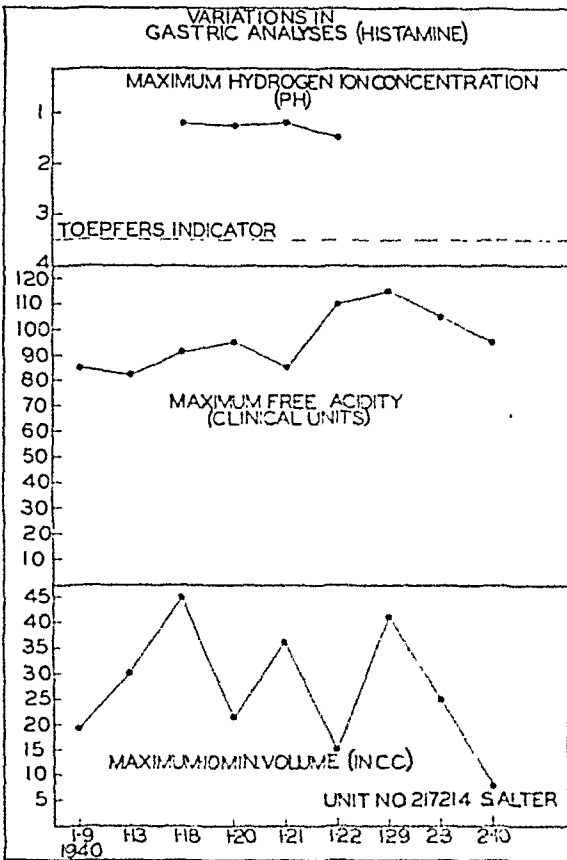


Chart 1, Case 1. Fairly constant maximum acidity (titratable and pH histamine) with marked fluctuations in the maximum ten minute volume in a patient with chronic gastric ulcer.

close the presence of free acid\* as is shown in the following table:

CASE No. 2

Date	Histamine	Free Acidity (Maximum)	pH
June 15	0.5 mg.	0	
15	0.5 "	0	
24	0.5 "	0	
25	0.5 "	0	3.49
30	0.5 "	52	1.50
30	1.0 "	76	1.50
30	1.0 "	68	1.61
	with 100 cc. of 7% alcohol		

In the third test the gastric position of the tube was checked fluoroscopically. The quantity and character of the material aspirated in the other tests, how-

\*The term "free acid" as used in this paper and as used generally indicates a hydrogen ion concentration sufficient to turn Toepfer's reagent (dimethylaminoazobenzene) red, i. e., a pH below 3.5. The terms "anacidity" and "achlorhydria" refer to a pH above 3.5. In this paper we are not concerned with the variations in pH above 3.5. (See Kirsner, J. B., Nutter, Paul B. and Palmer, Walter L.: Studies on Anacidity: The Hydrogen Ion Concentration of the Gastric Secretion, the Gastroscopic Appearance of the Gastric Mucosa, and the Presence of a Gastric Secretory Depressant in Patients with Anacidity. J. Clin. Invest., July, 1940.)

ever, were typical of gastric content. The histamine used was "Imido" (Roche) and was found to be effective in other patients at the same time. The dosage was 0.01 mg. per Kg. of body weight. The stomach was aspirated every ten minutes for sixty minutes after the subcutaneous injection. The three tests carried out on June 30 all disclosed the presence of acid gastric juice.

Chart 2 (Case 3) shows the variations seen in seven tests performed at intervals over the course of a year in a male patient (Unit 220303) 41 years of age with patchy atrophic gastritis as seen gastroscoically, with a tendency to moderate persistent diarrhea, but without other symptomatic or objective evidence of disease of any kind. Free acid was found in only 3 of the tests, the maximum value noted being 38. The gastric position of the tube was checked fluoroscopically during the last examination.

Chart 3 (Case 4) shows the variations observed in 28 examinations over a period of two years in a male patient (Unit 68973) 51 years of age with a chronic recurring gastric ulcer. Complete anacidity was found in 6 of the 28 examinations, the gastric position of the tip of the Rehfuess tube being checked fluoroscopically in 3 of the 6 negative tests. In the other tests the free acidity ranged from 5 to 83.

A similar phenomenon is to be seen in Chart 4 (Case 5). The patient (Unit 148736), a female 63

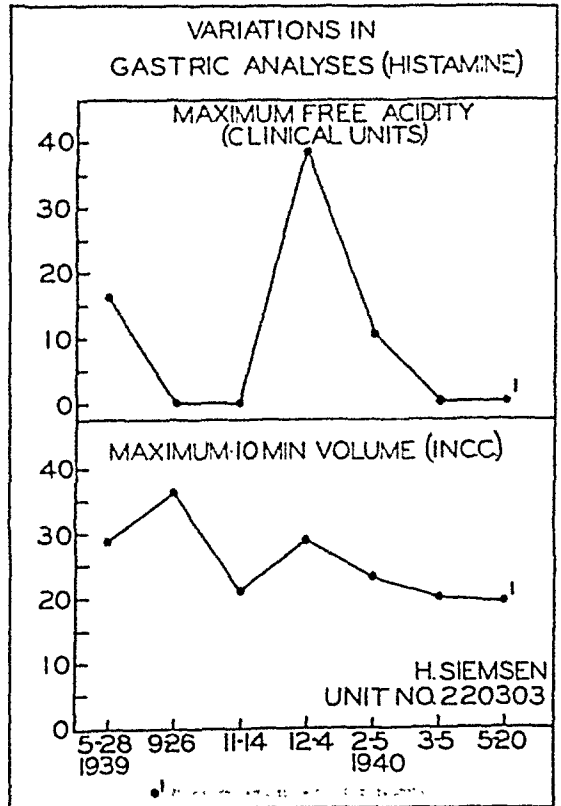


Chart 2, Case 3. Variations in the volume and free acidity after histamine observed in a patient with patchy atrophic gastritis and moderate diarrhea, but without other evidence of organic disease.

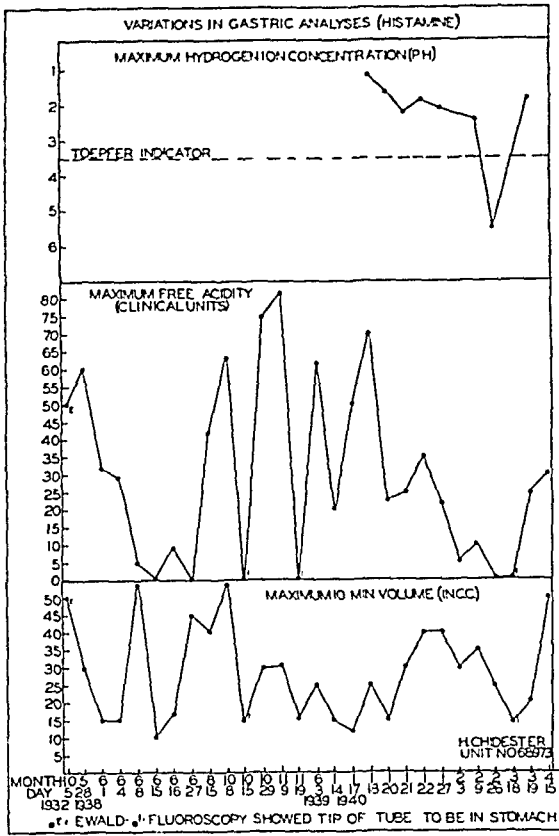


Chart 3, Case 4. Variations in maximum gastric acidity in a patient with chronic gastric ulcer.

years of age with a recurring gastric ulcer, underwent 48 examinations during the course of two years. The maximum free acidity varied from complete anacidity in 13 tests, in four of which the gastric position of the tube was checked fluoroscopically, to peaks covering almost the entire range between 3 and 58. The maximum hydrogen concentration likewise varied from a pH of 1.75 to 5.75.

In patient No. 6 (Unit 165135) Chart 5, a female 63 years of age admitted in December, 1936, with a large gastric ulcer, the same variation may be noted as is seen in Chart 5. In 39 analyses the free acid ranged from zero in 8 determinations, in four of which the gastric position of the tube was checked fluoroscopically, to 65 and 75. The relationship of these variations to gastric ulcer has been discussed elsewhere. (Palmer and Nutter)

The basis for these wide fluctuations in gastric secretion is not apparent. There was no definite correlation between the phases of anacidity and the severity or type of gastritis seen gastroscopically (7). This is in accord with Schiff's experience. There was no evidence of avitaminosis in any case although the patients with gastric ulcer were all on diets. Their diets, however, were adequate and we have, indeed, scores of control observations made in other patients consuming "ulcer diets" for years without any appreciable change in gastric secretion. There is no theoretical reason to attribute the refractory state of the acid secreting cells to psychic inhibition, and, in fact,

no overt change in the "nervous state" of the patients was noted during the phases of achlorhydria (8).

Apparently these cells may develop a spontaneous and transient refractoriness to histamine stimulation. Whether this is due to structural, hormonal, or

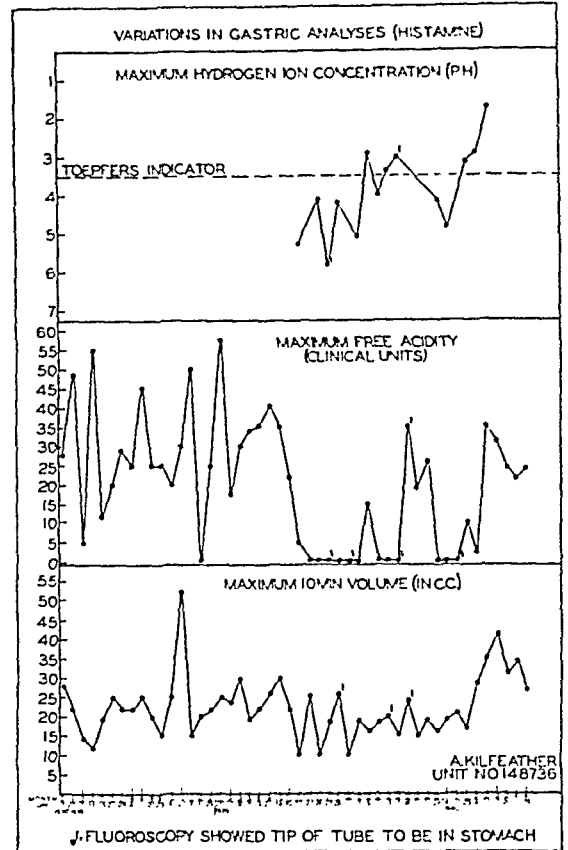


Chart 4, Case 5. Variations in maximum free acidity (titratable and pH) and in volume after histamine in a patient with recurring gastric ulcer.

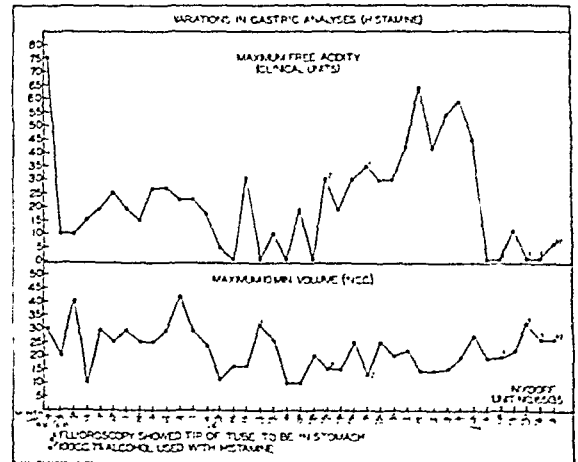


Chart 5, Case 6. Variations in maximum free acidity (titratable and pH) and in volume after histamine in a patient with recurring gastric ulcer.

nervous changes is unknown. It should be recalled, however, that a similar transitory, refractory state may be induced by roentgen irradiation, that the mucosa during such periods may appear normal gastroscopically, and that nevertheless structural changes have been demonstrated microscopically in the cell after radiation. There is, therefore, reason to suspect that these variations may not be entirely functional in origin (9).

### CONCLUSIONS

1. Although the gastric secretory curve in response to histamine is, in a given individual, quite constant as a rule, remarkable unexplained variations do occur.

2. "Histamine-proved" achlorhydria is not necessarily true anacidity. Great care is needed to exclude technical errors such as an incorrect location of the tip of the tube, excessive regurgitation of duodenal content, or the swallowing of saliva.

3. "Histamine-proved" achlorhydria is not necessarily permanent anacidity, for transient refractoriness to histamine does occur. The cause of this phenomenon is not known.

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### DISCUSSION

DR. MARTIN E. REHFUSS (Philadelphia, Pa.): I just wanted to inject a few remarks on this particular subject for the simple reason that when you study gastric secretion over a very long period of time in individuals, performing something like forty or fifty tests on the same individual, you will find variations that practically are inexplorable.

We studied two hundred students over eight years and many of those students had a repeated series of gastric tests. There would be a change in the secretion, for instance, a difference in free secretion, and there were variations in many of these patients.

In studying histamine, I feel there are unusual factors such as are encountered in chronic gastritis. The gastric secretion, after all, is nothing more than the functional output of the mucosa, and that mucosa may vary from day to day—for instance, in talking about gastritis, we get away from the fact that most studies, like gastroscopy, are studies of mucosal patterns, and it is what is happening underneath the mucosal pattern that counts, and I feel that there are definite changes. I am certain if you study the gastric secretion of anybody in this room over any length of time, you will see marked variations in the free acidity.

More than twenty-five years ago there were very careful microscopic examinations made on mucous membrane in an attempt to formulate differences in free acidity.

I should like to call attention to the fact that the more frequently you see people and make repeated gastric ex-

aminations, the more likely you are to see the changes that take place.

I should like to finish by mentioning one factor very interesting to us. We had a student who took a chemical examination and he failed in that chemical examination. We put milk into his stomach, and milk normally digests in a very characteristic sort of fashion. Most people don't realize that milk curds in two or three minutes in the normal human stomach. During the examination time we gave him a gastric test, and the milk came out precisely the way it went in, no curdling, no change, and no free acid in that man's stomach.

He then went off on the farm and came back later on and took his examination in the fall, and before we gave him his examination, we gave him again a complete milk study, and he digested milk perfectly. There was not only curdling but also normal gastric digestion of the milk, which is the characteristic phenomenon.

I feel that we are measuring the end result of the work of the mucous membrane, and I don't believe a single examination with histamine is sufficient. My objection to it is that it gives the stomach nothing to do but mucosal work. That is why a test meal is necessary. It gives the stomach mechanical work, the mucosal work, everything—and I think these ought to be considered in any estimation of such findings.

PROFESSOR BORIS P. BABKIN (Montreal): We have also observed in animals (dogs and cats), as you have observed in man, that the response of the gastric glands to histamine as well as to different test meals is very variable. In order to obtain a uniform secretory reaction the animal must be kept on a standard diet. The following factors are of very great importance: the amount of sodium chloride added to the food; the amount of water which the animal receives or loses; the vitamin intake, etc. Only when uniform conditions of nutrition are strictly maintained will repeated histamine tests give a more or less stable secretory response in animals as well as in man. If there are even slight variations in the diet, the same secretory stimulus may not produce the same result.

DR. GEORGE B. EUSTERMAN (Rochester, Minn.): Inasmuch as Dr. Babkin has made observations from the basic standpoint of experimental and applied physiology, I think it expedient to state our clinical convictions on the subject. Most of us will agree that the findings of paramount importance on gastric analysis are achlorhydria and undue retention of gastric contents. I am thoroughly in accord with the views of the essayist that an achlorhydria consistently refractory to histamine is incompatible with the diagnosis of active chronic gastric or duodenal ulcer. Under such circumstances a gastric lesion is either nonexistent or is not the familiar chronic benign ulcer.

The association of achlorhydria with a bulbar defect is an ever present problem for the gastro-enterologic internist. Under such circumstances I admonish that one must not be too quick to assume that one is in the presence of an active duodenal ulcer. A consistent histamine refractory achlorhydria, under the circumstances, also must make one first rule out a defect from causes extraneous to the duodenum, error in roentgenologic interpretation, or a healed lesion which is not playing a rôle in the patient's complaint. Rodgers and Jones, at Bart's in London, have described shallow subacute ulcers of the stomach in association with atrophy of the gastric mucous membrane and frequent achlorhydria. But such lesions, strictly speaking, are not comparable with those under discussion. Hurst also has reported cases of chronic calloused ulcer in association with achlorhydria in which the "free" acid returned after gastric lavage with solutions of hydrogen peroxide, as allegedly occurs in cases of chronic gastritis. Until convinced to the contrary I re-

gard such instances as apparent rather than actual achlorhydria.

DR. FRANKLIN HOLLANDER (New York, N. Y.): Mr. President, I should like to add some further evidence to the discussion—this time physiological and on human subjects without gastric disturbances.

In the course of our various secretory studies during the last few years on human subjects, we have made it a point to run at least two control test-meals before doing any sort of experimental procedure on the subject. Some of these data have been collected on ourselves and on technicians in our laboratory, and some on patients who are in the hospital for various conditions other than gastric. Frequently we have been able to do as many as four or five of these control analyses, using a 7 per cent alcohol solution as test substance.

It happens sometimes that of several such gastric analyses, done at intervals of several days to a week, one of them will yield a completely anacid curve. This sort of thing has happened with surprising frequency, and in apparently normal subjects, but in all instances we find a complete loss of acidity on one day with a return of

secretory response several days later. We have never been able to give any satisfactory physiological explanation for these observations.

DR. WALTER L. PALMER (Chicago, Ill.): First I want to thank the gentlemen for their discussion, and then to take one minor point of disagreement with my good friend, Dr. Eusterman. If I understood him, he said Avery Jones and Rogers reported chronic—

DR. EUSTERMAN: Subacute.

DR. PALMER: Oh! I want to further emphasize that point and I suspect the explanation he gave of Hurst's cases with achlorhydria. As he pointed out, these cases were those in which achlorhydria was found on one or two tests, but on which the acid returned, probably without reference to the irrigations with peroxide.

Finally, with regard to the subject of ulcer and achlorhydria, may I again remind you of the large series of autopsy studies of patients with pernicious anemia—the number runs well over a thousand, without a single case of chronic ulcer having been found.

## Comparative pH Values Within the Stomach, Pylorus and Duodenum in Antacid Therapy\*

By

JAMES B. EYERLY, M.D.  
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THE effect of antacids in the treatment of gastric and duodenal ulcerations has been the subject of much debate. These substances have been used not only to relieve pain but also to neutralize the gastric content and inhibit peptic digestion. Information obtained from aspiration samples as to the extent of acid reduction, X-ray studies and clinical improvement have been our chief means of evaluating treatment. Such a complex of factors enters into the average ulcer problem that the value of inhibition of gastric digestion alone is difficult to determine. We have not been satisfied that aspiration samples give adequate information as to gastric acidity (1, 2) because (1) gastric content is incompletely mixed; (2) it is most acid in the antral region; (3) aspiration of material for a test disturbs the gastric or intestinal content, and (4) a representative sample of any one region is difficult to obtain.

To measure the hydrogen ion concentration in situ we have devised a glass electrode which can be placed in the antrum of the stomach, pylorus and the descending portion of the duodenum.

### METHOD OF PROCEDURE

An electrometer with a special electrode, as previously described (1), was used. Improvements have been made, however, in the cap over the glass bulb of the electrode (Fig. 1). Flexible rubber is substituted for the original hard protection. The terminal rim which supported the fingers of the original cap is removed and free circulation about the bulb is possible.

These soft rubber fingers are kept in place by threads which are fastened to their tips and tied together with equal tension at a point 2 cm. distal to the glass bulb. Two centimeters distal to this knot the ends of the threads are fastened to a round metal weight 0.5 cm. in diameter. This weight sinks the electrode into the gastric content, facilitates entry of the unit into the duodenum and acts as an anchor after the desired position is reached. When testing gastric content the threads are shortened so that the weight is only 1.5 cm. from the glass bulb, and readings may be ob-

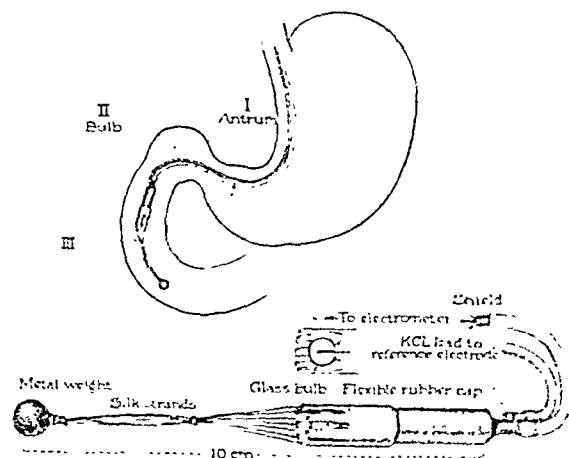


Fig. 1. Diagram showing the stomach and duodenum with the three positions in which test readings were made. Lower figure shows the glass electrode used in detail.

\*Presented before the American Gastro-Enterological Association, Atlantic City, N. J., June 10-11, 1940.

\*From the Gastro-Intestinal Department of Presbyterian Hospital.

tained in the antrum without permitting the weight to lodge in the pylorus.

The results shown were obtained in two patients who had no organic disease of the stomach or duodenum. The desired positions of the electrode were first located by fluoroscopy; marks were placed at the points where the lead wire passed the incisor teeth. In subsequent tests the alkalinity of the duodenum and the marks on the lead wire were used in determining the position of the electrode.

Most satisfactory and speedy entry of the unit into the duodenum was obtained in the fasting state, with the patient lying on his right side and the knees flexed upwards. A pH above 5 and occasional light tugs on the lead wire indicated that the electrode was in the duodenum and the desired position was chosen. When testing in the antral region the patient remained in the prone position on his right side. After the electrode was placed the test substance was given and in thirty or more minutes readings were begun. Each test period lasted two hours and readings were taken at five minute intervals.

Except in the fasting control periods in which nothing was given, the indicated amount of antacid and three ounces of whole milk were given alternately at half hour intervals preceding and during the test period. The usual dose of each antacid was given in three ounces of water. Mucin was thoroughly mixed in water before using and the magnesium trisilicate removed from its capsule; both these procedures facilitated optimum neutralization.

In both patients the distance from the incisor teeth to the glass bulb in the antrum was 19½ inches

(Position I); to the duodenal bulb 22¼ inches (Position II), and lower descending portion of the duodenum 25½ inches (Position III) (Fig. 1).

## RESULTS

1. *Antrum of the stomach:* (Position I). In patient A. H. all antacids raised the pH above that obtained in the fasting state. Less neutralization occurred in patient N. L. B., and in two tests using mucin and magnesium trisilicate, values below the fasting state were found. When milk alone was taken every half hour a higher pH was found than when it was alternated with any of the other antacids except the tribasic powders and calcium carbonate in A. H. Calcium carbonate was very effective for A. H. but not so helpful to N. L. B., and almost the opposite holds true for sodium bicarbonate. These substances are readily dispersed and react rapidly. Amphojel and magnesium trisilicate react slowly and apparently have less effect unless retained long enough; fair neutralization was accomplished with the latter in A. H. (Chart 1)

2. *Pylorus:* (Position II). The fasting values shown are much the same as those obtained in the antrum of the stomach. The general average on antacid therapy is to a higher pH than was obtained in the stomach. More complete mixture of antacid and regurgitation may be responsible for this difference. Magnesium trisilicate and amphojel show the greatest change; sufficient time for reaction and more complete mixture probably account for the improvement. Mucin in both patients, amphojel in N. L. B., and milk in A. H. produced values little above the fasting state.

TEST	POSITION I		POSITION II		POSITION III	
	N.L.B.	A.H.	N.L.B.	A.H.	N.L.B.	A.H.
Fasting State	1.60	1.44	1.30	1.60	5.47	5.96
Tribasic Calcium Phosphate.....gr. XX	2.04	4.02	4.21	3.20	5.74	4.72
Tribasic Magnesium Phosphate.....gr. XV						
Calcium Carbonate.....gr. XV	1.70	3.28	2.66	3.63	5.37	5.13
Sodium Bicarbonate.....gr. XX	2.27	1.92	3.50	2.64	6.92	5.50
Aluminum Hydroxide (Amphojel) 10 cc.	1.81	1.88	1.80	3.09	5.17	3.54
Mucin (Armour & Co.).....10 gm.	1.33	1.88	1.56	1.71	5.56	4.09
Magnesium Trisilicate (Trisomin) gr. X	1.45	2.37	2.81	3.34	6.02	4.35
Milk.....3 ounces	2.40	2.90	3.42	1.82	5.82	4.03

Average pH values for patients N.L.B. and A.H. obtained over two hour test periods. Except in the fasting state, the test substance was given every hour and 3 ounces of milk were taken on the half hour

Chart 1. Comparative average pH values for various antacids in the stomach, pylorus and lower descending duodenum (positions I, II and III).

# FASTING STATE patient (N.L.B.).

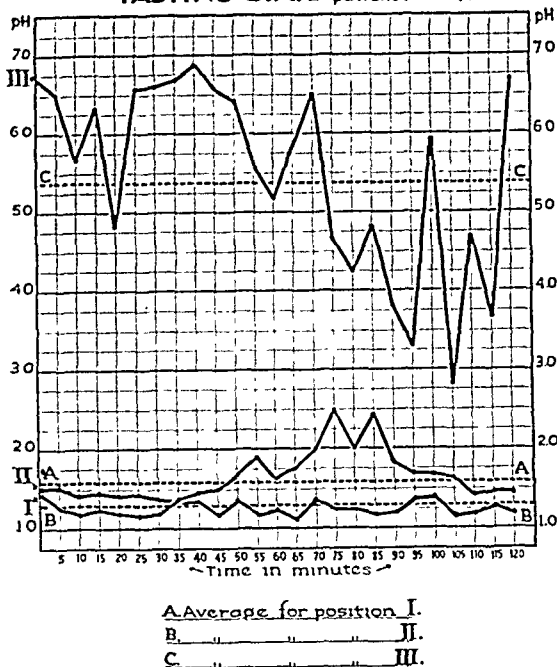


Chart 2. pH curves and their average values obtained when readings were taken every 5 minutes for 2 hours in the fasting state with the electrode in the stomach, pylorus and lower descending duodenum (positions I, II and III).

Tribasic powder, calcium carbonate and sodium bicarbonate raise the pH most consistently.

3. *Lower portion of the descending duodenum:* (Position III). The electrode is in the region of the ampulla of Vater and the alkaline secretions of the liver, pancreas and duodenum are evident. Frequently the average pH of a neutralization test period was lower than that of the fasting state. This was especially true in A. H., who had an average pH of 3.54 on amphojel compared to a pH of 5.96 in the fasting state. Possibly the increased flow from the stomach tends to raise the hydrogen ion concentration of the upper duodenal content faster than the alkaline secretion reduces it. One of the most interesting findings is that the pH of the duodenal content may be lowered in antacid therapy.

Frequently marked fluctuations in pH occurred rapidly in all positions tested. In the fasting state (Chart 2) only moderate changes occurred in the antrum and pylorus but a low pH, 2.8, and a high pH, 6.7, within fifteen minutes were observed in the duodenum. A characteristic series of curves as obtained with antacids is shown in Chart 3. In each position consistent acid reduction is shown and if the peaks of neutralization are compared it will be noted that they correspond quite uniformly and an idea of the rate of passage of the antacid is obtained.

## DISCUSSION

We believe that a method of accurately determining the pH of gastric and duodenal content in a relatively undisturbed state is now available. By this means the effectiveness of antacid therapy and the usefulness of various antacids can be critically determined.

In some of the tests shown and in several others obtained on patients receiving supposedly adequate neutralization therapy, unsatisfactory acid reduction is found when measurements are made in situ. Such findings lead us to believe that antacid therapy has not yet had a fair trial if reduction of acid corrosion and inhibition of peptic digestion promote the healing of an ulcer.

Individuals without demonstrable organic disease were chosen so that comparable results could be obtained in each test. We do not wish to imply that the averages shown can be used as standards. Many more such tests are necessary to evaluate antacids. It is unlikely that duplicate tests several days apart will be the same but in general they should be similar. These results show that by present standards we are unable to predict with any accuracy the effect of an antacid without studying its reaction within the digestive tract.

In a previous report we demonstrated active egg white digestion in the antral region of the stomachs of several patients on what had been considered adequate neutralization therapy. When by means of gastric electrode measurements an antral pH of 3.5 or more could be maintained, no measurable egg white digestion took place. Hollander (3) states that pH 5 or more must be maintained to avoid peptic digestion. This latter figure is rather high and it is unlikely that this level is reached and maintained in many patients receiving neutralization therapy.

## CONCLUSIONS

1. The pH of the gastric and duodenal content of man can readily be determined in situ.
2. There are rapid and marked fluctuations in the pH of gastric and duodenal content in the fasting state as well as when antacids are given.
3. Antacids in general raise the pH of the gastric and pyloric content.

# ULCER MANAGEMENT patient (N.L.B.).

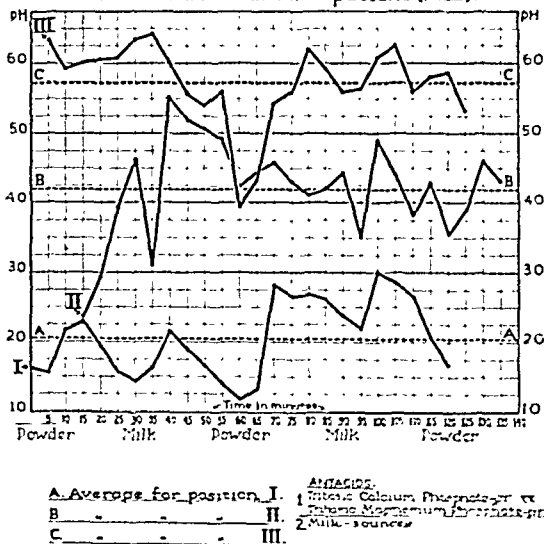


Chart 3. pH curves and their average values obtained when patient N. L. B. was given tribasic powders and milk at alternate half hour intervals. Readings taken every 5 minutes for 2 hours.

4. In antacid therapy the pH of the duodenal content may be lower than that of the fasting state.

5. Neutralization therapy consisting of 20 grains of tribasic calcium phosphate with 15 grains of tribasic magnesium phosphate on the hour and three ounces of milk on the half hour produced the most satisfactory pH elevation.

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#### DISCUSSION

DR. RALPH C. BROWN (Chicago, Ill.): I have but a word to say. I can't discuss this from the technical standpoint. To me the most interesting feature of this work is that it demonstrates a means whereby accurate pH readings can be obtained continuously over as long a period of time as may be desired in the stomach or duodenum.

It has been recognized, of course, that the titration of aspirated samples yields results which are only approximately correct. The elevation of intragastric pH to a point where peptic digestion ceases certainly is not the sum total of ulcer therapy, but there is rather general belief to the effect that the annulment of peptic action in the gastric juice plays an important role in what we try to do for ulcer patients. If this be true, then we must welcome any procedure which will supply us with accurate information as to the fluctuations that may take place in the pH levels from hour to hour as we administer to patients various types of alkalies.

DR. L. C. MCGEE (Elkins, W. Va.): The question of pH in the gastro-intestinal tract is interesting and will lead ultimately, I think, to surprising findings so far as

the small bowel is concerned. During the past winter with the use of the Miller-Abbott tube, in contradistinction to determination of pH in situ, we have found that the fasting contents of the small bowel prefers a pH lower than that of blood. This is not attributable entirely to hydrochloric acid entering the jejunum from the stomach because in instances of persistent achlorhydria, as in patients having pernicious anemia for years, the pH in the intestine is on the acid side. Such a reaction persists in an isolated segment for a period of hours in the jejunum. In addition one finds carbon dioxide tensions which are much higher than may be found in the blood.

The reason for these findings is, so far as I am concerned, not obvious. It is to be hoped that the pH observations in situ may give sufficient data for a logical explanation of this very peculiar change in the reaction of the small bowel as compared with other fluids of the body.

DR. JAMES B. EYERLY (Chicago, Ill.) (closing the discussion): Our findings locally are quite similar to those which have been found before by intubation. Of particular interest is the marked changes that occur. There is a rapid fluctuation at times in the pH curve, both in the fasting state and when antacids are used. Changes that may occur from day to day in identical tests are of interest. Drs. Hollander, Palmer and others have demonstrated such changes in various studies.

Our study was limited entirely to the measurement of pH. Many variables not ordinarily considered are brought to attention in such a study. No specific information as to the amount of acid secreted and degree of dilution is determined. Gastric tonus, peristaltic activity and retention are also unknown. The role played by duodenal regurgitation is not clear. Only the resultant of all these factors on gastric and duodenal pH is measured.

## The Correlation of Antral and Bulbar Pressures With Fluoroscopic Observations During Gastric Evacuation\*

By

J. P. QUIGLEY, Ph.D., J. M. WERLE, M.D.

and

DANIEL BRODY, M.D.  
CLEVELAND, OHIO

WE have devised a method employing optical manometers for accurately recording intralumen pressure from the alimentary canal. This method appears to be particularly well adapted for the study of pressures which result in propulsion through the digestive tract or develop from spastic states in the gut.

We applied this method to an investigation of the mechanics of gastric evacuation in trained dogs. We combined determinations of the pressures developed at either end of the pyloric sphincter with fluoroscopic studies of antral and bulbar contractions, the time of passage of material through the sphincter and the degree of approximation or separation of lead shot fastened to the serosa at either side of the sphincter.

This investigation led to the conclusion that gastric

evacuation results from a basal pressure in the pyloric antrum 3-5 cm. of water in excess of the bulbar pressure. During early evacuation, a peristaltic wave involves the antral region, but the sphincter and duodenal bulb are relaxed. As the wave progresses the sphincter and bulb contract, a phasic pressure wave develops in the antrum and in bulb, evacuation continues briefly then ceases and bulbar contents are propelled distally, antral and bulbar pressure waves are of about the same magnitude, usually they vary between 15-30 cm., but occasionally pressures in excess of 60 cm. of water are recorded. The antral phasic wave is associated with the second period of gastric evacuation, and the bulbar wave with bulbar emptying.

The pyloric sphincter is relaxed during most of the evacuation cycle. The phase of the cycle during which it contracts makes the sphincter very effective in preventing duodenal regurgitation, but its direct in-

\*From the Department of Physiology, Western Reserve University Medical School.  
Read at the Annual Session of the American Gastro-Enterological Association at Atlantic City, N. J., June 10-11, 1940.  
Aided by a grant from the Council on Pharmacy and Chemistry, American Medical Association.

fluence in preventing gastric evacuation would appear to be slight. Minor variations in the time of antral and bulbar contractions occur but usually bulbar contraction follows antral so definitely as to indicate that the relationship is not fortuitous.

### DISCUSSION

DR. WILLIAM OSLER ABBOTT (Philadelphia, Pa.): Two points lead me to discuss this interesting paper of Dr. Quigley and his associates: In the first place we have been carrying on somewhat comparable observations on the pressures in the intestine of normal human subjects at the University of Pennsylvania, and have absolute pressure readings taken simultaneously from three points which agree sufficiently closely with these he has just shown us to constitute confirmation within the probable limits of species difference.

The second point is the more important and the one on which I should like to dwell, namely the importance which may attach to the type of work which Dr. Quigley has been reporting to us.

We speak of symptoms arising from lesions of the digestive tract, but the stimulus which we know will produce pain from the gut is pressure, and the movement of

content, as can be said of the movement of content in any system of tubes, is dependent on pressures.

Approximately half the patients who come to the gastro-intestinal section, do so because of pain associated with functional disorders, and I think it is a reasonable prediction that an understanding of the relation of changes in intraluminal pressure of the gut tract to the symptoms observed may throw light on the origin and nature of these disorders. In a like manner the determination of blood pressure in cardiovascular disease has brought to light such conditions as hypertension which cannot always be detected at the autopsy table.

DR. J. P. QUIGLEY (Cleveland, Ohio) (closing the discussion): I should like to thank Dr. Abbott for his remarks and I wish to add that in the past a great number of references have appeared in the literature regarding pressure in the lumen of the gut, but I am quite certain most of these determinations were erroneous. I feel now that we have a number of accurate intralumen pressure determinations, and, judging from the frequency with which previous investigators have shown an interest in intralumen pressures valuable results in the future may be anticipated from this accurate method.

## The Secretin Test in the Diagnosis of Pancreatic Diseases With a Report of One Hundred Thirty Tests\*

By

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and

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NEW YORK, NEW YORK

### INTRODUCTION

By

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DR. DIAMOND was probably the first investigator in this country to utilize the new secretin technic in the clinical study of the pancreas. What this new method means for clinical medicine in general and for gastroenterology in particular can be best realized when we contrast the previous status of pancreatic diagnosis with what now lies open before us. The situation may be compared to the era before and after the introduction of the gastric test meal.

Before the "secretin era" the only exact knowledge we had about pancreatic secretion was obtained by intubating the pancreatic duct in experimental animals. In the intact human being, however, we had no precise conception of what the pancreas was doing. We did not know anything about the basal secretion of the gland. We had no standard stimulus with which to obtain pancreatic juice at will. We used arbitrarily selected foods or chemicals; and what we got was a mixture contaminated with gastric secretions and bile. We had no concept of a standard experimental period and therefore no uniform method of withdrawing a specimen reproducible under standard conditions. In short there was no way for establishing a norm for pancreatic function.

Now, thanks to the secretin test and the double lumen gastro-duodenal tube we can obtain pure pancreatic juice, uncontaminated by stomach contents and free from bile. We can first isolate the basal pancreatic output. We can then administer a specific hormone quantitatively and almost instantaneously by intravenous injection, thereby creating on demand a standard test secretion. And finally, since the duration of the reaction is known, we can demarcate a standard test period during which it is possible to collect the total output of the pancreatic gland.

It is obvious from the foregoing that the work of Dr. Diamond and his collaborators has opened up many rich new fields, not only in the diagnosis of pancreatic disease, but in the experimental physiology of the pancreas, and ultimately, I am confident, in the therapy of pancreatic ailments as well. It therefore gives me great pleasure to introduce Dr. Joseph S. Diamond, who will tell us something about "The Secretin Test in the Diagnosis of Pancreatic Diseases."

The study of functional disorders of the pancreas received little attention from the clinician until recent times. The chief interest in diseases of the pancreas centered around the problem of acute pancreatitis, its etiology, diagnosis and methods of treatment. Chronic lesions were regarded as rare and many vague abdomi-

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EFFECT OF SECRETIN UPON  
CONCENTRATION OF ENZYMES  
(AVERAGE OF NORMAL CASES)

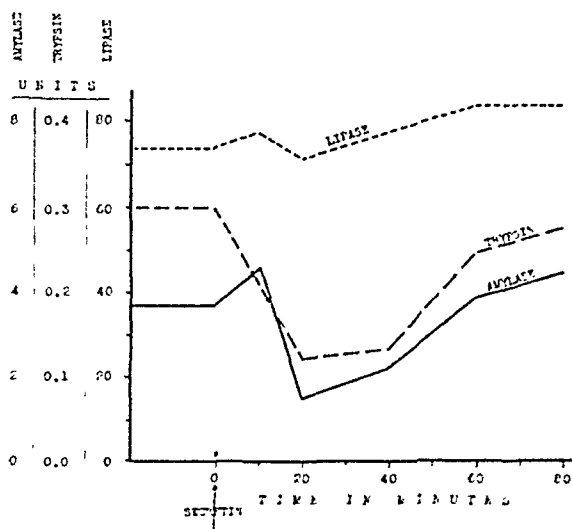


Fig. 1

nal and digestive symptoms were never correlated with diseases of the pancreas.

Little was known of the effect on the external secretion of the pancreas of systemic diseases such as lues, chronic alcoholism, neoplasms and other general toxins. Little was also known of the effect on the production of chronic lesions of the pancreas arising from the reflux of bile into the pancreatic ducts in cholelithiasis and diseases of biliary apparatus associated with infection and sphincter spasm. Recent studies by means of cholangiograms with opaque media, by Colp and Doubilet (1), and Leven (2), have revealed the ready interplay between the bile and pancreatic juice. In Leven's series the pancreatic duct was visualized in 23% of the ninety-one patients examined. Colp and Doubilet also found the presence of amylase in the bile in 28.5% of their cases. The authors also found marked amylase and lipase activity in the bile obtained from a cholecystostomy fistula in a case of acute hemorrhagic pancreatitis.

The relation of the pancreas to steatorrhea also remained obscure. In this connection one might mention the work of Andersen (3) who has collected autopsy reports of forty-nine cases of cystic fibrosis of the pancreas, which were unrecognized during life and were regarded as coeliac disease.

The function of the external secretion of the pancreas in diabetes, cirrhosis of the liver, tumors, cysts, traumatic lesions, penetrating gastric and duodenal ulcers was also little known. The reasons are obvious: (a) the anatomical location of the gland and the difficulty of palpation, (b) the inaccessibility of its secretion, (c) the lack of a standard stimulus to the pancreas and (d) the inability of obtaining from the duodenum a pure uncontaminated pancreatic juice.

With the introduction of Secretin by Hammarsten and Agren (4, 5) and the use of the double lumen gastro-duodenal tube, these difficulties have now been overcome.

In Secretin\* we possess a pure substance, free from histamine and cholecystokinin. When injected intravenously in a standard dose it causes a marked increase in the secretion of pancreatic juice. The flow reaches 150 cc. or more in one hour and is rich in bicarbonate, concentration and the enzymes: amylase, trypsin and lipase.

In a previous report (6) we have described at length the method of carrying out the test. By using a double lumen gastro-duodenal tube we are able to obtain pure uncontaminated pancreatic juice through the prevention of admixture of gastric and duodenal juices. Briefly it may be mentioned that the free end of the double tube is permitted to enter as far as the third portion of the duodenum, while the shorter end, attached 10 inches higher, remains in the stomach. Under fluoroscopic guidance in the upright position the tube is quickly advanced to the pylorus and with manual pressure upward at the greater curvature and antrum, the passage of the tube into the pylorus is facilitated. The period of duodenal intubation is thus considerably shortened.

With a negative pressure not exceeding 50 mm. of mercury the gastric and duodenal fractions are separately and completely collected. After collecting a basal flow for 20 to 25 minutes, when the duodenal juice becomes clear and is no longer contaminated with the acid gastric chyme, Secretin is injected intravenously (0.75 mg. per kilogram of body weight). We felt that by using the larger dose we were subjecting the gland to a maximal stimulus. We have also shortened the duration of the test to one hour from the previously reported 80 minute period.

Following the injection of Secretin the flow increases rapidly rising sharply in the first ten minutes and gradually declining, reaching its basal level at the

\*Astra Co., Sweden.

NEURO-HORMONAL MECHANISM  
INSULIN - SECRETIN EFFECT ON ENZYME CONCENTRATION

(16 Units Insulin Intravenously 30 Minutes Before Secretin - Blood Sugar 65 mg.)

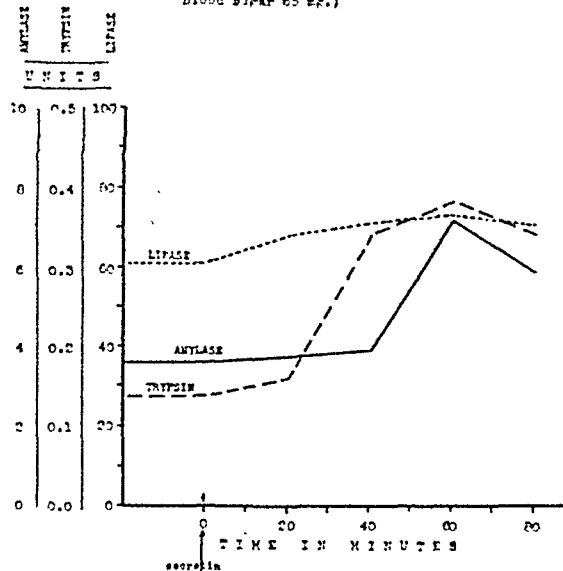


Fig. 2

end of 80 minutes. The total volume secreted varies from 150 to 250 cc. The flow which has previously been bile stained becomes colorless in a few minutes and remains so throughout the greater part of the test. A deeply bile stained secretion throughout the entire test period indicates a diseased or non-functioning gall bladder (7), whereas a clear opalescent juice indicates a normally functioning viscus, the bile entering the gall bladder and is stored there.

The bicarbonate concentration varies between 90 to 130 m.eq. per liter. The enzymes: amylase, trypsin and lipase, are quantitatively determined according to the methods previously reported (6) and are expressed in units per one hour period per kilogram of body weight.

The total amylase output for one hour varies between 300 to 1200 units. The total output of trypsin

ducts are first washed out. The concentration then falls to a low level due to the dilution by the large volume of fluid secreted, and then rises again toward the end of the test when the volume is diminished (Fig. 1). When, however, vagal stimulants such as insulin or acetylcholin or pilocarpine are used in conjunction with Secretin the concentration of the enzymes is maintained at a high level and the total output for the test period rises two to three times as high as when Secretin alone is used. This is best illustrated when a hypoglycemia is induced by the injection of 16 units of insulin intravenously one-half hour before Secretin is given (Fig. 2). Pancreatic secretion must, therefore, be regarded as dependent upon two factors comprising a *neuro-hormonal mechanism*. The hormone, Secretin, affects the volume and bicarbonate and the neurogenic factor, the vagus, affects the output of enzymes. Table I illustrates best this mechanism, showing the behavior of the concentration of the enzymes when Secretin is used alone and when combined with insulin.

It may also be stated that the effect of Secretin stimulation is dependent upon two factors: the total mass of pancreatic tissue and the functional capacity of its cells, whereas the enzyme output is dependent, in addition to the above, to the vagal tone.

#### MATERIAL STUDIED

The present report consists of 130 tests performed upon 104 individuals. In 20 cases the test was repeated from two to four times as follows: in 13 cases twice, in 5 cases three times, in 2 cases four times.

There were 24 normal individuals (Table II) and 80 pathologic cases. The normal cases included physicians, students, and others with unrelated ailments. In this group the results were uniform in all with the exception of three. These three students gave surprisingly low figures for volume and enzymes, the bicarbonate was low in one. We have nevertheless included them among the normals although on closer questioning we obtained a history of a chronic diarrhea during childhood in one. The other two gave a history of previous vague digestive disturbances. One of these had a slightly elevated blood Van den Bergh.

#### SECRETIN RESPONSE IN PATHOLOGICAL STATES

In the abnormal state of the pancreas all of its functions may become affected. The enzymes, especially lipase and amylase, seem to suffer first and become diminished in the milder disturbances of the gland. The volume and bicarbonate are more stable and are not easily disturbed, the bicarbonate least of all (Fig. 3). The lesion may produce dissociation of the enzymes where only one may be affected while the others remain normal. All, however, may become markedly diminished, as well as the volume and bicarbonate in severe lesions such as acute hemorrhagic pancreatitis with necrosis. This state may persist even long after the surgical recovery of the acute lesion and is apparently due to necrosis of a portion of the gland and its replacement by fibrous tissue. The end result is therefore dependent upon the diminished mass of the recovered gland and the functional capacity of the remaining cells.

TABLE I

*Neuro-hormonal mechanism*  
*Insulin-secretin effect on enzyme concentration*

Secretin			
	Amylase	Trypsin	Lipase
Basal	2.86 u.c.	0.22	77
	1.38	0.17	59
	1.59	0.09	47
	2.08	0.14	68
	2.24	0.06	72
	3.88	0.26	77
Insulin-secretin (Blood sugar—65 mg.%)			
	Amylase	Trypsin	Lipase
	3.6	0.14	61
	3.76	0.16	68
	3.88	0.34	71
	7.12	0.38	73
	5.84	0.34	70

varies between 20 to 40 units. Lipase varies between 7,000 to 14,000 units.

The quantitative evaluation of the normal function of the pancreas for the one hour test period consists of the following:

Volume—135 to 250 cc. (2.1 cc. to 4.5 cc. per Kg./60')

Bicarbonate—90 to 130 m.eq.

Amylase—300 to 1200 u (5.5 to 11 u/Kg./60')

Trypsin—20 to 40 u (0.35 to 0.7 u/Kg./60')

Lipase—7000 to 14000 u (135 to 225 u/Kg./60')

#### THE NEURO-HORMONAL MECHANISM

The total volume and bicarbonate concentration run in parallel curves and vary directly to the amount of Secretin injected. The behavior of the enzymes differs from that of the volume and bicarbonate. Their concentration does not vary in proportion to the Secretin dosage. The enzyme output appears to be dependent also upon the vagus tone. When Secretin is injected intravenously the preformed enzymes stored in the

*The pathological material consists of the following:*

Cholelithiasis .....	17
Pancreatitis .....	3
Hemorrhagic pancreatitis with fat necrosis .....	1
Edema of the pancreas .....	1
Chronic pancreatitis .....	1
Obstructive jaundice .....	6
Carcinoma of the head of the pancreas....	3
Carcinoma of the biliary ducts .....	2
Atresia of the common duct .....	1
Cysts of the pancreas .....	3
Cirrhosis of the liver with lues .....	3
Splenomegaly with lues .....	1
Toxic hepatitis (2 with lues) .....	5
Acute yellow atrophy of liver (lues) .....	1
Steatorrhea .....	15
Pernicious anemia .....	1
Diabetes .....	4
Colitis—ulcerative .....	3
Miscellaneous .....	18
Postcholecystectomies, duodenal ulcer, spontaneous cholecystoduodenal fistula, chronic nephritis, etc.	

### I—CHOLELITHIASIS (Table III)

Seventeen cases of cholelithiasis were examined. Fifteen came to operation. Five had stones in the common duct, with jaundice. One developed liver abscess, two associated with diabetes, one of which had acute edema of the pancreas, and one case with inter-

mittent attacks of fatty stools and diarrhea. All of the cases which presented complications revealed varying degrees of pancreatic deficiency. Five presented low amylase; three had low trypsin; five had low lipase; two had low volume and two had low bicarbonate. Seven uncomplicated cases gave normal figures.

### II—PANCREATITIS (Table IV)

One case of hemorrhagic pancreatitis was examined seven weeks after the operation while still discharging from a cholecystostomy sinus. The findings indicated a marked deficiency in all the functions including volume, bicarbonate and enzymes. Some of the enzymes were as low as one-eighth to one-fifteenth of the normal. The pancreatic juice was admixed with considerable pus. Subsequent examinations made four months and ten months later revealed considerable improvement in the function. The output, however, of the volume and enzymes still remained half of the normal.

The case of chronic pancreatitis presented several attacks of recurrent jaundice. Examination with Secretin during one of these episodes revealed low bicarbonate, amylase, lipase and also a high blood lipase.

The patient with edema of the pancreas, who had long-standing diabetes and cholelithiasis, presented a typical clinical picture of marked left upper quadrant tenderness and high blood amylase and lipase. A Secretin study three weeks afterwards, when apparent clinical recovery had taken place, showed low bicarbon-

TABLE II  
Normal cases. Secretin test — 80'

Name	Wt. Kgm.	Volume		Bicarb. Meq.	Enzymes (u. Per Kgm.)			Duod. Ict. Index	Serum Van D. Bergh
		Total cc.	cc. Kgm.		Amylase	Trypsin	Lipase		
S. S.	69	250	3.6	88	9	.4	155	0	
M. G.	71	179	2.5	126	6.1	.46	172	0	
M. G.		175	2.47	117	10.4	.45	177	0	
S. G.	64	137.8	2.15	128	3.8	.3	121	0	
R. W.	91	277	3.04	96	11.1	.59	159	0	.4
B. W.	57.7	160	2.8	106	13.7	.78	160	0	1.6
J. S.	47.7	116	2.4	90	12.9	.84	159	5	.4
J. C.	58.2	154	2.6	103	11.2	.47	185	0	1.1
M. L.	65.9	210	3.2	106	12.3	.57	190	0	.4
J. F.	62	98	1.58	130	8	.09	121	0	
J. F.	62	141	2.3	109	9.6	.39	215	0	
J. V.	66.6	260	3.9	103	6.47				
M. H.	63	145	2.3	98	6.33	.48	166	0	
I. H.	57	179	3.1	112	7.75	.5	220	0	
C. B.	61.5	131.5	2.1	125	18.8	.28	169	0	1.3
S. K.	67	179	2.67	84	6.68	.59	168	0	
J. L.	63	149.5	2.57	107	13.4	.81	173	0	
I. I.	77.2	174	2.25	116	7.4	.4	167	0	
I. E.	60	220	3.66	114	12	.51	183	2	.9
J. M.	64.5	185	2.9	108	15.3	.8	172	8	.4
B. M.	61.4	226	3.7	106	9.4	.75	233	0	.2
H. B.	76	99.2	1.3	50	3.9	.22	67	0	
M. B.	66	68.7	1.04	108	4.4	.19	60	0	
A. H.	77.2	132	1.7	108	5.8	.27	86	0	1.8

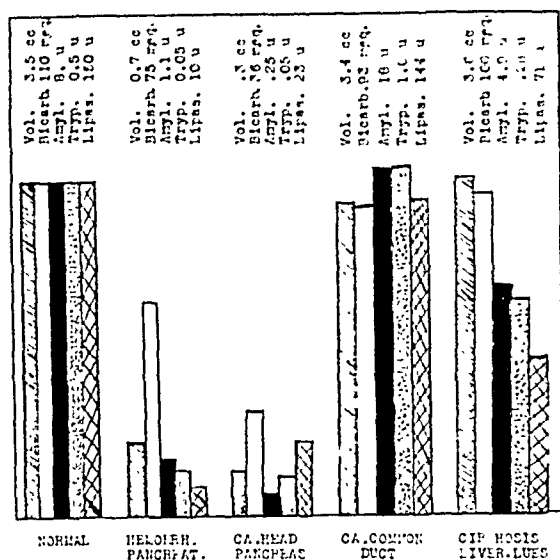


Fig. 3. Abnormal response to secretin in various pathologic states of the pancreas.

ate and very low normal figures for amylase and trypsin.

### III—OBSTRUCTIVE JAUNDICE (Table V)

This group includes three cases of carcinoma of the head of the pancreas, two cases of carcinoma of the biliary ducts and one case of atresia of the common duct post-operatively. All of these cases were operated upon with the exception of one case of carcinoma of the head of the pancreas. One case of carcinoma of the head of the pancreas came to autopsy.

These three cases of carcinoma of the pancreas

showed marked deficiency in the function of the pancreas. The tests were performed twice. In one instance all the enzymes were entirely absent and the bicarbonate output was as low as 10 m.eq. per liter. In the second case the autopsy revealed the tumor so situated that it compressed the common duct but not the pancreatic duct. Here we found a diminished volume and a marked diminution in the trypsin and lipase output. The third patient, who was not operated upon, presented a clinical picture of unmistakable diagnosis. A large, hard, immovable mass was felt in the left upper quadrant, producing in the X-ray a pressure defect in the stomach. There was also a distended, palpable gall bladder. The first test showed practically no response to Secretin. The second test, four months later, showed considerable free blood in the duodenal contents with mitotic cells seen under the microscope. The Secretin injections in this instance were followed by colicky pains of short duration.

In the group with carcinoma of the biliary ducts the operation revealed one with a primary lesion in the common bile duct and the second, carcinoma of the hepatic ducts. The Secretin test gave entirely normal findings in the common duct lesion, indicating a non-involved pancreas and a patent pancreatic duct. In this instance the test was of great value in definitely ruling out a pancreatic lesion. The second also gave normal volume and bicarbonate, showing only a slight diminution in the amylase and trypsin.

In the atresia of the common duct post-operatively, the test was performed four times. In all instances the test gave normal pancreatic findings.

### IV—CYSTS OF THE PANCREAS

There were three cases of cysts of the pancreas. All were operated upon. One was examined while still in

TABLE III  
Cholelithiasis. Secretin test — 80°

Name	Date	Wt. Kgm.	Volume		Bicarb. M.eq.	Enzymes (u. Per Kgm.)			Duod. Ict. Index	Serum Van D. Bergh
			Total cc.	cc. Kgm.		Amylase	Trypsin	Lipase		
E. G.		65.9	423	6.4	96	14.3	.38	224	25	1.4
T. B.		60.5	232	3.8	110	8.6	.6	268	57	.5
M. H.		64	244	3.8	114	9.9	.54	305	23	.6
E. B.		58.5	171	2.9	110	5.2	.76	219	0	
G. W.*	Stone C. D.	42.3	232	5.5	88	5	.88	412	27	4.1
S. B.		61.8	167	2.7	110	13	.75	100	2	.6
M. M.	Stone C. D.	72.7	262	3.6	72	8.1	.9	310	33	4.1
L. B.	Stone C. D.	94.5	234	2.5	114	7.1	.38	20.2	0	4.8
F. H.	Stone C. D.	84	160	1.9	108	3.4	.26	120	0	6.8
M. L.		59	197	3.3	82	6.6	.4	248	25	1.2
A. L.	Stone C. D.	77.3	125	1.6	105	7	.21	93	0	3.5
		77	114	1.48	114	5.9	.21	82	0	3.8
		72.7	159	2.1	91	10.4	.4	118.4	1	1.8
E. S.	Liver Absc.	68.2	345	5.1	98	6.6	.71	133	30	9.
M. L.	Fatty Diarr.	54	160	2.7	110	6.8	.49	114	0	.6
F. C.	Diab.	74.1	410	5.5	60	15	1.1	225	23	1.5

TABLE IV  
*Pancreatitis. Secretin test — 80'*

Name		Date	Wt. Kgm.	Volume		Bicarb. M.eq.	Enzymes (u. Per Kgm.)			Duod. Ict. Index	Serum Van D. Bergh
				Total cc.	cc. Kgm.		Amylase	Trypsin	Lipase		
M. B.	Acute Hemorrh.	6/26/39	60	43.5	.7	75	1.1	.05	10.1	puru	.4
		9/27/39	60.9	101	1.7	62	1.16	.24	126	75	.4
		2/28/40	68.2	90	1.3	86	3.1	.26	80	.80	.4
H. S.	Chronic Paner.		56.8	180	3.2	80	3.9	.63	117	0	12
M. L.	Edema Paner.		59	197	3.3	87	6.4	.4	40	75	1.2

the hospital with a persistent pancreatic fistula. This patient showed marked interference in function, the juice being collected from the duodenum as well as from the fistula. When the test was repeated five weeks later the results showed some improvement, still, however, below normal.

The other two cases showed only moderate interference in function.

#### V—CIRRHOSIS OF THE LIVER

There were three cases of cirrhosis of the liver, two with positive serology. They were fairly advanced cases with ascites, splenomegaly and one was jaundiced. In these two instances the pancreatic function was markedly disturbed, all enzymes being diminished. The third case was a milder form with negative serology, with ascites and a palpable spleen. This patient responded favorably to therapy, the ascites disappearing. The test here showed only diminished bicarbonate but no interference with the volume or enzyme output.

#### VI—SPLENOMEGALY

In one case of splenomegaly with lues and a secondary anemia, only the lipase was diminished. Otherwise the findings were normal.

#### VII—TOXIC HEPATITIS

There were five cases in this group: two complicated with lues. In these two instances the Secretin test revealed marked disturbance in the pancreatic function with diminution of enzymes. In one of these cases the test was performed four times with similar findings even after the jaundice had cleared. In the

other three cases the tests were normal. In only one case, of the more severe type, the lipase was diminished.

#### VIII—ACUTE YELLOW ATROPHY OF THE LIVER

There was one case of acute yellow atrophy of the liver. This patient came to the hospital with jaundice which developed after neoarsphenamin treatment for lues. Symptoms were moderate at first and the patient received the usual treatment with intensive glucose therapy and sodium thiosulphate. The Secretin test was performed during this period. It revealed a marked deficiency, affecting all the functions, the volume, bicarbonate and all the enzymes. The following day the patient became drowsy and listless. The cholesterol was low; the ester dropped to zero. The patient rapidly developed the typical clinical picture of acute yellow atrophy and succumbed five days later. The autopsy confirmed the clinical diagnosis. The pancreas revealed edema and slight fibrosis but no necrosis. Evidently the depressed function was due to the same toxin.

#### IX—STEATORRHEA

There were fifteen cases of steatorrhea comprising eight very severe forms requiring hospitalization and six milder ambulatory types. All these patients were subjected to thorough clinical investigation including quantitative fat studies in the stool, hematological studies, blood chemistry, roentgen studies of the gastro-intestinal tract and bones.

TABLE V  
*Obstructive jaundice due to carcinoma. Secretin test — 80'*

Name	Diag.	Date	Wt. Kgm.	Volume		Bicarb. M.eq.	Enzymes (u. Per Kgm.)			Duod. Ict. Index	Serum Van D. Bergh
				Total cc.	cc. Kgm.		Amylase	Trypsin	Lipase		
A. L.	Ca. Head Paner.	10/ 9/39	51.8	131	2.5	10.	0	0	0	83	10.5
M. G.	Ca. Head Paner.	10/25/39	68.2	132	1.95	114	7.3	0.12	29	35	18.4
		11/ 1/39	66.4	190	2.8	108	9.4	0.34	120	2	13.8
R. P.	Ca. Head Paner.	12/21/38	52	17.5	0.3	20	0.25	0.05	23	110	9.2
		4/17/39	53	96	1.78	35.8	2.02	0.24	83	0	11.5
O. K.	Ca. Com. Duct	6/ 5/39	68.1	234	3.4	93	18	1.0	144	0	6.4
C. T.	Ca. Hepa. Duct	10/24/38	54.5	132	2.4	118	5.4	0.31	190	2	17.6
G. T.	Ca. Stom. Metast.	10/ 6/38	71.0	65	.92	59	10.1	0.2	43		

The clinical picture was that of sprue and they were so regarded. The severe forms presented frequent, large, bulky, fatty stools with marked nutritional disturbances, emaciation and anemia. The milder forms presented vague digestive symptoms and intermittent attacks of diarrhea, in whom, however, the nutritional disturbances were not marked.

The Secretin studies revealed as follows: In ten cases, including six severe types and four ambulatory, there were varying degrees of pancreatic deficiency involving particularly the lipase. In addition, five also showed low volumes; one—low bicarbonate; two—low amylase; five—low trypsin. All ten showed lipase deficiency. In the remaining five cases, four of which were very severe forms and one ambulatory, the pancreatic function was entirely normal as to volume, bicarbonate and all enzymes. In five instances the test was repeated from two to four times.

We feel that the five cases which showed normal pancreatic function can be regarded as cases of sprue or idiopathic steatorrhea, while the other cases which showed such profound lipase deficiencies may be regarded as steatorrhea associated with pancreatic lesions. In the very severe forms which received active treatment with diet, transfusion and liver therapy, with the improvement of the patient the pancreatic function also showed restoration to normal values. In this connection it may be stated that in Andersen's series of 49 cases of cystic fibrosis of the pancreas the clinical picture during life was that of coeliac disease.

The similarity of the clinical picture in the steatorrheas makes the condition a difficult one for differential diagnosis and the readiness with which one can be mistaken for the other becomes obvious. In Secretin we have a fairly simple procedure which provides a sharp line of differentiation between the cases of steatorrhea showing normal pancreatic function and those in whom the pancreatic function is deficient.

#### X—DIABETES

There were four cases of diabetes. Two were associated with gall stones and one entered the hospital with acute edema of the pancreas with high blood amylase and lipase. The Secretin test was performed after clinical improvement when the diabetes was under full control with insulin and dietary regime. The findings revealed in one case a low lipase and in the other two cases low bicarbonate. Two cases, in addition, had non-functioning gall bladders. One case gave normal findings.

#### XI—MISCELLANEOUS

This group included four cases in whom cholecystectomy had been performed. All responded normally to the Secretin test. One case of spontaneous cholecystoduodenal fistula showed a lowered bicarbonate; otherwise normal. One case had a markedly enlarged and hard liver and revealed a low bicarbonate and low lipase. This group also included four young men with digestive disturbance and negative gastro-intestinal findings. The Secretin test showed in all cases deficient function involving the volume, trypsin and lipase in each; the amylase in three and the bicarbonate in one. In two patients the test was repeated with similar results. Another patient in this group was a young man who suffered from attacks of syncope. During one of these episodes a blood sugar revealed a hypoglycemia

of 50 mg. Inasmuch as a possible adenoma of the pancreas was suspected the Secretin test was performed and repeated after an interval of three weeks. All the functions except the bicarbonate were markedly diminished in both tests. The final diagnosis as to the nature of the lesion still remains unconfirmed.

#### SUMMARY AND CONCLUSIONS

Secretin, given intravenously in dosage of 0.75 mg./Kg. of body weight, causes a marked response in the flow of pancreatic juice. The use of a double lumen gastro-duodenal tube provides a clear uncontaminated juice rich in bicarbonate and enzymes.

The external secretion of the pancreas may be regarded as governed by a neuro-hormonal factor. The volume and bicarbonate secretion is directly proportional to the amount of Secretin injected while the production of enzymes is dependent in addition upon a neurogenic or vagal tone. When Secretin alone is injected, pancreatic juice of low enzyme concentration is elaborated. When insulin or other vagal stimuli are used in conjunction with Secretin the enzyme concentration is increased two to three fold.

In severe lesions of the pancreas all functions are simultaneously involved and become markedly diminished. In milder forms the enzyme production is the first to suffer. The volume and bicarbonate are more stable and are less easily disturbed.

The enzymes may become dissociated so that one may become more affected than another.

A series of one hundred and thirty tests have been carried out in one hundred and four patients, of whom twenty-four were normal and eighty comprised pathological conditions.

The test supplied us with valuable information of disturbed function of the gland in chronic states that hitherto were unrecognized and unsuspected. In cholelithiasis with common duct stones the pancreas became simultaneously affected revealing various degrees of disturbed function. In obstructive lesions when the pancreatic duct is encroached upon from growths developing in the proximity of the duct the test has supplied diagnostic data through a diminished or totally absent response, depending upon the extent of blockage of the duct. In lues the test seems to show a depressed function of the pancreas. This likewise occurs in cirrhosis of the liver, chronic alcoholism, acute yellow atrophy of the liver and the graver forms of toxic hepatitis. In the steatorrheas the test has been most valuable in indicating the presence of pancreatic deficiencies and has helped to differentiate between the idiopathic group including sprue and those with pancreatic lesions. In the follow up studies in the steatorrhea group the test has shown the reversibility of the function and has been consistent with the clinical improvement of the patient indicating the degree of recovery.

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### DISCUSSION

DR. JAMES T. PILCHER (Brooklyn, N. Y.): I think this test which these gentlemen have developed, and brought to our attention, is extremely interesting and instructive, but it pertains more to the ascertaining of discrepancies in the output of pancreatic juice, and refers more to chronic than to acute conditions.

I have been more particularly interested in one or two cases which they have experimented with, particularly the instance of acute hemorrhagic pancreatitis and incidence in another of acute edema of the pancreas, which I assume they did not attempt to test during the early stages of either of these cases.

I should like to know, indeed, whether, during the acute phase of these conditions, they attempted the introduction of a duodenal tube and, in addition, a stomach tube also. These patients are alarmingly ill, as you all know, and it does not seem feasible to me to entertain the procedure which they have suggested.

I should like to know, however, if in these two cases, if the experimenters and the essayists have determined the other, much more easily recovered materials which are diagnostic, and, particularly, I am referring to the amylase in the blood in conjunction with that secreted in the urine.

During the past year I have encountered two instances of acute abdominal emergencies in which a differential diagnosis was made by this determination, which prevented me from exploring, even these cases; and which were subsequently proven, after the primary shock had passed, to be instances of acute pancreatitis.

I should like to know if they have any statistics relative to these two conditions, to compare with their procedure.

DR. MANDRED W. COMFORT (Rochester, Minn.): I have been interested not only in Dr. Diamond's presentation this morning but also in his published articles on his experience with secretin as a stimulant of external pancreatic secretion.

My own interest in secretin as a stimulant of external pancreatic secretion began with a publication by Greengard and Ivy in 1934, giving the first record of the use of secretin in treatment of a large series of human beings. It seems to me that a number of points concerning secretin and its use deserve emphasis: (1) that the secretin now available commercially can be given without any reaction; (2) that the dose has been standardized and reproducible results are possible; (3) that it is a potent stimulant of external pancreatic secretion and should prevent the occurrence of false, low total values for the various fractions in the duodenal contents; (4) that it discloses marked disturbances of pancreatic secretion as well as dissociated disturbances of secretion of volume, carbonate and enzymes, and (5) that secretin alone, of all the stimulants which so far have been used for study of external pancreatic

secretion, has given information of value regarding the secretion of carbonate.

Secretin as a stimulant of external pancreatic secretion has certain shortcomings. Since the range of variation among normal persons is so wide, mild disturbances of function will not become apparent, and since secretin causes a decrease rather than an increase in concentration of enzymes in the duodenal contents, it does not reveal the concentrations at which the pancreas is capable of secreting the enzyme.

I have been reminded by the discussion of histamine, heard this morning, that ten years ago some of those who were using histamine at that time thought that it was an ever constant gastric stimulant. Today we know that it is not. I am wondering whether ten years' experience with secretin will disclose that it also will fail to produce a constant secretory response.

DR. JOSEPH S. DIAMOND (New York, N. Y.): I wish to thank Dr. Kantor for his interest in our work and his introductory remarks. I also wish to thank Drs. Pilcher and Comfort for their interesting comments. The test lends itself mostly to subacute and chronic states. The case of acute hemorrhagic pancreatitis which we studied, was examined several weeks after the patient was operated on. Our experience with cases of acute pancreatitis has been limited. We shall have to see in the future how feasible it is to introduce a tube in the acute stage to carry out pancreatic studies.

In the very large group of chronic diseases and in those with vague and unexplained abdominal symptoms, the test can be done very simply. We have reduced the procedure to one hour and it does not upset the patient in the least. As you also heard from Dr. Comfort, the secretin itself is absolutely harmless and produces no ill effects upon the patient, occasionally only a temporary flushing.

With regard to the effect of secretin upon the blood enzymes, I wish to say that we have had the opportunity to study the blood enzymes before the injection of secretin and again one-half hour after the injection of secretin. These results have not been published as yet, but we can state here that the pharmacological effect of the injection of secretin in the normal state is to produce a rise in the blood enzymes. This rise may reach twice as high as the previous figure. The elevation may be even more striking in pathological instances except in those cases where there is a marked depression in the activity of the pancreas when the blood enzymes are originally very low. In these instances we find no change in the blood enzyme curve after secretin.

Regarding Dr. Comfort's remark about the lowered concentration of the enzymes in the pancreatic juice after secretin, I wish to say that, if quantitative estimations are made for the entire hour period, we find that the total output of the enzymes rises considerably as compared to the basal state. The concentration becomes lower on account of the great dilution from the increased volume which may reach 150-250 cc. during the hour. When we experimented with vagal stimulants in conjunction with secretin, the concentration of the enzymes then rose considerably. This latter procedure is not, however, necessary for the ordinary clinical purposes.

# The Presence of Spirochetes In Human Gastric Mucosa

By

A. STONE FREEDBERG, M.D. (by invitation)

and

LOUIS E. BARRON, M.D.\*

BOSTON, MASSACHUSETTS

IN 1893 Bizzozero (1) reported the presence of spirochetes in the gastric mucosa of the dog and stressed the occurrence of these organisms in the parietal cells. Later reports agreed with these observations (2, 3). Krienitz (4) in 1906 found spirochetes in the stomach contents of patients with ulcerating gastric carcinoma. This was confirmed by Luger and Neuberger (5) who in addition noted the rarity of these organisms in the gastric mucosa and gastric juice of normal individuals. Recently Doenges (6) reported that spirochetes could be found in the gastric glands of 43 per cent of human stomachs examined in the routine of autopsies. The question arises whether these organisms are natural inhabitants of human gastric mucosa or are just post-mortem or agonal saprophytic invaders.

Therefore we confined ourselves to a histologic investigation of human gastric mucosa made available from gastric tissue resected for duodenal or gastric ulcers or for carcinoma.

The purpose of this paper is to report the results of our studies.

## METHODS OF INVESTIGATION

Gastric tissue was obtained from thirty-five patients who were subjected to partial gastric resection; nineteen had carcinoma of the stomach; fourteen had duodenal and two had gastric ulcers. The Wassermann and Kahn reactions of the blood were negative in all patients. The tissue was stained with hematoxylin and eosin, and in addition by the silver impregnation methods of deGalantha (7) and DaFano (8). The latter, while ordinarily used to demonstrate the Golgi apparatus, was extremely satisfactory for outlining the spirochetes in the gastric mucosa of the dog (9). The results with the three different staining techniques were similar except that the silver impregnation methods outlined the spirochetes more clearly.

In order to study the influence of room temperature as well as body temperature on the rate of growth of spirochetes in the mucosa, tissue was obtained from two stomachs, one of which had chronic gastritis associated with duodenal ulcer, and the other had carcinoma at the pylorus. In both cases tissue was removed from the pylorus as well as from three and nine cm. proximal to this. These various segments were prepared for microscopic study by three different techniques: (1) immediate fixation and staining by the hematoxylineosin, and the silver impregnation methods of deGalantha and DaFano; (2) tissue was exposed to room temperature for three, seven, eleven and twenty-one hours respectively before fixation and staining;

(3) tissue was incubated at 37 degrees centigrade for the same periods just noted and stained by the same techniques.

## RESULTS

In the gastric mucosa obtained from 35 patients, spirochetes were found in 13 patients, an incidence of 37.1 per cent. This approximates the figures published by Doenges (43 per cent) (6). However the incidence

TABLE I

Diagnosis	Number of Cases	Cases Positive	% Cases Positive
Carcinoma	19	9	47.3%
Gastric ulcer	2	2	100%*
Duodenal ulcer associated with chronic gastritis	14	2	14.2%

\*Average of 21 gastric ulcerations (malignant and benign), 11 positive = 52.3%.

of these organisms in stomachs with benign and malignant ulcerations was greater than in those in which there was no ulceration. Thus organisms were found in only 14.2 per cent in non-ulcerating stomachs as compared with 52.3 per cent where ulceration was present. Since only two cases of benign gastric ulcers were studied, we can attribute no special significance to the high percentage noted (Table I).

TABLE II

Diagnosis	Number of Cases	Number of Slides	Positive Results Number of Slides	Percentage Positive Slides
Gastric carcinoma	19	90	16	17.7
Gastric ulcer	2	16	3	18.7
Duodenal ulcer associated with chronic gastritis	13	54	2	3.7

Although 52.3 per cent of the gastric ulcerations revealed the presence of spirochetes, it should be emphasized that the organisms were found with difficulty and frequently required long and careful search through many slides. Thus from tissue obtained from 18 out of 19 cases of gastric carcinoma, 90 slides were prepared. Spirochetes were found in only 16 slides or 17.7 per cent (Table II). The greatest number of spirochetes were invariably present either in areas of

\*From the Departments of Pathology and Medical and Surgical Research, Beth Israel Hospital, Boston, Mass.  
Read at the Annual Session of the American Gastro-Enterological Association, Atlantic City, N. J., June 10-11, 1940.



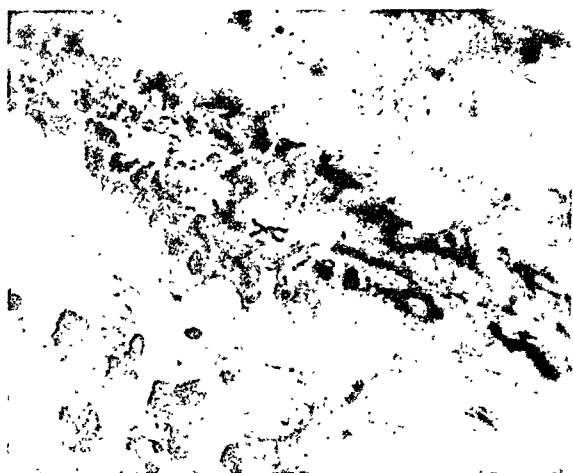


Fig. 1. Silver impregnation, DaFano technique. 970x. Spirochetes in the lumen of a gastric gland. The tissue was obtained from a case of gastric carcinoma.

extensive necrosis, or in the lumina of glands of contiguous mucosa but never within the cellular portion of the tumor (Fig. 1).

Gastric mucosa from 13 cases of chronic gastritis associated with duodenal ulcer was prepared for microscopic study and fifty-four slides were satisfactory. Spirochetes were found in only two slides or 3.7 per cent (Table II). In both instances the organisms were found only in the lumina of the glands in the most superficial layers of the mucosa, in contrast to the observations made in the dog in which the spirochetes were found throughout the thickness of the mucosa as well as within the canaliculi of the parietal cells (Fig. 2).

Eighty-one slides were prepared from tissue which was left at room temperature and incubated at 37 degrees centigrade respectively for three, seven, eleven and twenty-one hours. One case had carcinoma of the pylorus and the other had duodenal ulcer associated with mild chronic gastritis. Twenty-four slides were made directly from the carcinoma. In this group spirochetes were noted in eleven slides, 45.8 per cent. Twelve slides prepared from three and nine cm. proximal to the carcinoma were entirely negative for spirochetes. In the case of duodenal ulcer also used in this study, 45 slides were prepared out of which only four were positive, 8.9 per cent. It was noted here that spirochetes were only found after the tissue had been incubated or kept at room temperature for seven, eleven, or twenty-one hours (Fig. 3).

Sixteen slides were prepared from two cases of benign gastric ulcer. Three slides were positive, 18.7 per cent. In each instance the spirochetes were found in the tissue at the periphery of the gastric lesion.

#### COMMENT

The presence of spirochetes in the gastric mucosa of certain laboratory animals is now established. In 1919 Kasai and Kobayashi (3) noted these organisms in the dog, cat and monkey. Edkins (10) found a high frequency of spirochetes in the gastric mucosa of the cat, but noted a marked decrease in the number of organisms in the fasting state. This observation may help to explain the necessity for prolonged search

through numerous slides in the detection of organisms in surgical specimens. The prolonged preparation preceding gastric surgery such as abstinence from food, strict attention to oral hygiene, and frequent gastric lavages may not only interfere with the growth of the organisms but may actually eliminate them from the gastric contents.

From our results it does not seem likely that spirochetes are natural inhabitants of normal human gastric mucosa. Although 37.1 per cent of the total number of patients revealed the presence of organisms, they were not found with the same abundance as noted in the gastric mucosa of the dog. In our material it very often was necessary to search through many slides prepared from the same specimen in order to find one slide which revealed organisms, and very often this slide contained only a few spirochetes. This is substantiated by the data in Table II which indicated that the number of slides containing spirochetes in relation to the total number of slides examined is extremely low. Furthermore these organisms in our experience were only seen within the lumina of the glands in the most superficial portion of the mucosa. None were noted in the canaliculi of the parietal cells.

Our results would seem to indicate that spirochetes are found with increasing frequency in the presence of necrotizing malignant or benign ulceration. The converse is true; in the absence of ulceration, spirochetes are rarely found. There was no evidence in our specimens indicating that these organisms have any pathogenic significance.

In the tissue subjected to incubation and exposure to room temperature for varying periods of time, very little influence was noted on the growth and number of organisms. In the stomach with carcinoma, spirochetes were found only in those sections taken directly from the tumor. In sections taken three and nine cm. away, that is, microscopically normal mucosa, spirochetes could not be demonstrated.

In the other case, in a search through 45 slides, only four revealed the presence of organisms, approximating the results obtained in unincubated similar tissue (Table II).

In a survey of the illustrations noted in the various reports, the spirochetes in the mucosa of the experi-

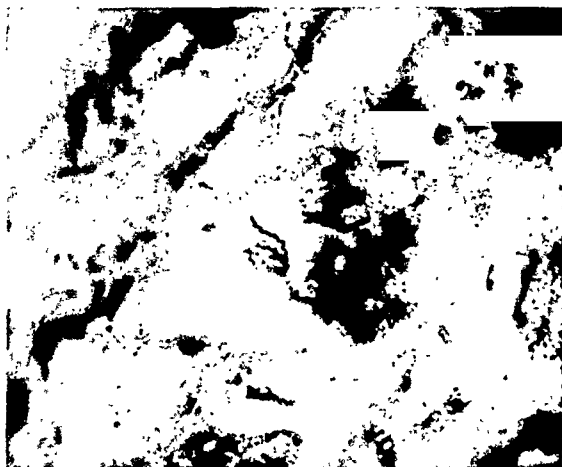


Fig. 2. Untuned silver impregnation, DaFano technique. 970x. Spirochetes in the gastric mucosa of a dog.



Fig. 3. Silver impregnation, DaFano technique. 970x. The tissue was obtained from a case of chronic gastritis and was incubated at 37 degrees centigrade for 11 hours.

mental animals leave no question as to their identity. This was not always the case with the illustrations purporting to demonstrate spirochetes in human gastric mucosa. This was successfully obviated by the silver impregnation methods referred to previously.

### CONCLUSIONS

1. Spirochetes are rarely found in the mucosa of gastric tissue resected for duodenal ulcer without attendant gastric ulcerations.
2. They are frequently found in those stomachs whose mucosa is diseased by malignant or benign ulcerations. In these instances they are found in or close to the lesion.
3. The silver impregnation method of DaFano will demonstrate spirochetes in the gastric tissue of the dog and human.
4. Incubation and exposure to room temperature for varying periods seemed to exert very little influence on the number of spirochetes in human gastric mucosa.

We wish to express our appreciation to Dr. Monroe J. Schlesinger, in whose department this work was carried out. Mrs. Edith Herman rendered valuable technical assistance.

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### DISCUSSION

DR. FRANK D. GORHAM (St. Louis, Mo.): Dr. Barron's and Dr. Freedberg's report of their results in a search for spirochetes in the gastric mucosa of pathologic human stomachs is interesting.

More and more there is a tendency to separate the possible causative factors of acute cyclic peptic ulcer from the factors of chronicity of some peptic ulcers that refuse to heal under usual ulcer management. In this latter group I have used over a period of some ten years bismuth (Bismoid), administered intramuscularly, with encouraging results.

Some four years ago, when searching for a pharmacological explanation of the therapeutic action of bismuth in chronic ulcer, one of the possibilities which suggested itself was that in chronic ulcer one of the factors of chronicity might be an associated infection by an organism thriving best in an acid (hydrochloric acid) medium. At that time my attention was directed to some investigations of Dr. Cowdry, of the Washington University School of Medicine.

Cowdry and his coworkers, Scott and Doenges, were finding in the stomachs of Macacus rhesus monkeys, spirochetes in the cytoplasm of the parietal cells and in the lumen of the gastric glands, and in some instances associated with localized inflammatory changes.

I obtained for Dr. Cowdry some human stomachs which he studied. Later Doenges examined some 242 well preserved stomachs removed at autopsy, finding spirochetes in some 43 per cent. These spirochetes were not found in the glands of the intestinal mucosa, suggesting that their habitat was specifically the stomach. Also this organism was not Vincent's, neither was it *Spirochaeta pallida*, but an unidentified spirochete.

From their investigation, Dr. Cowdry and his coworkers could not definitely establish any etiological relationship between the presence of the spirochetes in the mucosa of the stomach and serious gastric pathology.

All investigations to date tend to corroborate Dr. Barron's and Dr. Freedberg's conclusions that the role of spirochetes in gastric disease has not been established; however, I believe that a further search should be made for an organism thriving in hydrochloric acid medium (and variations of hydrochloric acid are normal in all stomachs) as a possible factor of chronicity, if not an etiological factor, in peptic ulcer.

DR. LOUIS E. BARRON (Boston, Mass.) (closing the discussion): The results of our studies on resected stomachs were similar in many ways to those reported by Dr. Doenges for stomachs removed at autopsy. There are, however, certain minor differences.

In our experience spirochetes were found with great difficulty. Frequently it was necessary to prepare a large number of sections before one or two revealed organisms.

Furthermore, in order to prevent erroneous interpretation of artifacts, our slides were examined by other members of the laboratory and a unanimous opinion was reached before a slide was considered positive for spirochetes.

We cannot substantiate the view that spirochetes, stained by the routine hematoxylin-eosin stains, can be detected with ease. In our experience it was necessary to use the silver impregnation techniques to outline the organisms.

# Abstracts of Current Literature

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## CLINICAL MEDICINE

SCATENA, R.: *La ptyalina en la saliva del recién nacido y del lactante. (Ptyalin in saliva of new born and lactating infants).* Rev. Soc. Argentina Biol., 15(7):360-363, 1939.

Ptyalin was found in nearly all new born babies, even when premature. Up to the 5th month diastatic activity varied between 400 to 600 units (Wohlgemuth's technique), from 6 to 12 months it was found between 2,400 to 2,700. The individual variations were considerable. Twins (8 pairs) did not have the same conc. of ptyalin, neither did triplets (1 case). The taking of food did not modify the conc. of ptyalin in the saliva. Breast fed infants had higher concs. than those artificially fed and those on a mixed diet had the highest ptyalin conc.—J. T. Lewis (Courtesy of Biol. Abst.).

ORBAN, B. AND WEINMAUN, J. P.: *The Cellular Elements of the Saliva and Their Possible Role in Caries.* J. Am. Dental Ass'n, 26(12):2008-2017, 13 figs, 1939.

A study was made on the cellular elements of saliva. These are composed of epithelial cells and leucocytes. The saliva of caries-immune mouth have more epithelial cells and fewer leucocytes than the caries-active mouth. In the caries-immune mouth there is more cellular-bacterial activity than in the susceptible mouth, which suggests a new field of research in the problem of dental caries.—D. C. Lyons (Courtesy of Biol. Abst.).

SIMONS, DONALD J.: *The Diagnosis and Therapy of Gastric Crises.* Am. J. Syphilis, Gonorrhea and Venereal Dis., 23(6):782-796, 1939.

Simons reviews the classification of types, etiology, symptomatology, differential diagnosis and treatment of gastric crises. The pathology of gastric crises remains to be determined and the origin of the pain is still unknown. While the specific treatment of tabes dorsalis is only moderately effective, relief or material lessening of the severity of the symptoms may be obtained by routine treatment in 69% of cases. Fever therapy, chordotomy, and resection of the gastric twigs of the vagi may be necessary in resistant cases.—D. C. Smith (Courtesy of Biol. Abst.).

SCHINDLER, RUDOLF: *The Incidence of the Various Types of Gastric Disease as Revealed by Gastroscopic Study.* Am. J. Med. Sci., 197(4):509-516, 1939.

Statistics on the incidence of gastric diseases in the United States and in Europe are presented, based upon gastroscopic findings in 1000 and 255 patients. There are apparently no marked geographical differences in the distr. of gastric diseases.—Auth. summ. (Courtesy of Biol. Abst.).

LATTIMORE, J. L., GOLD, A. AND EBENDORF, H. C.: *The Wilhelmj Test Meal.* Am. J. Clin. Path. Tech. Suppl., 4 (1):24-26, 1940.

The test meal is prepared in paste form in collapsible tubes by the Difco Laboratories and keeps at least 8 months. Weigh about 5 gm. to the nearest 0.1 gm. and add 46 cc. of water for each gm. The conc. of phenol red 446

should be 15 mg. per liter. For single samples use 200 cc. of test meal and 500 for a fractional series. Centrifuge two 5 cc. samples, one for estimation of phenol red and the other for acidity. "Free" and "Combined" acids are of no significance. For total acidity add 5 cc. of sample to 75 cc. of distilled water. Heat on a steam bath for 30 minutes and titrate with N/20 NaOH using 4 drops of 0.4% alc. bromocresol purple. Correct for the acidity of the original meal as determined by a similar titration. Compare the conc. of phenol red in the test meal and in the gastric sample by adding 1 cc. of 10% NaOH to 5 cc. of sample, stand 15 minutes, centrifuge, and compare in a colorimeter. Reading of test meal/Reading of gastric sample  $\times 100 = \%$  of meal in the sample. If bile is present compensate by adding a few crystals of picric acid to the test meal standard before comparing. Total acidity of the stomach contents—acidity of the test meal  $\times \%$  of test meal in the stomach contents = corrected acidity of the stomach contents. Corrected acidity of the stomach contents  $\times 100/100 = \%$  of the test meal in sample = acidity of pure gastric secretion.—G. H. Chapman (Courtesy of Biol. Abst.).

SCHINDLER, RUDOLF: *Importance of the Gastroscope in the Diagnosis of Gastric Diseases in the Army.* Brit. Med. J., 1940(4128):243-247, 1940. Cf. Ibid. p. 260.

These two articles show the advances made in gastroscopy since the safe Wolf-Schindler flexible gastroscope was invented in 1932. Records of 13 cases are given, with illustrations, describing the conditions revealed by the gastroscope in chronic gastritis, gastric ulcer, tumor and normal mucosa. The findings are discussed and their significance noted in the diagnosis of true disability and malingering.—J. B. Paton (Courtesy of Biol. Abst.).

JORGENSEN, MYRON N., DIETZ, NICHOLAS AND HILL, FREDERICK C.: *Potassium as a Toxic Factor in Intestinal Obstruction.* Proc. Soc. Exp. Biol. and Med., 43(2):282-287, 1940.

This report presents data from expts. in which the whole blood and plasma K levels were measured on dogs, before, and at intervals throughout the period of survival of dogs suffering from intestinal obstruction produced surgically. Normal whole blood K values observed on 15 dogs varied from 17.6 to 37.2 mg. % with an average of 23.5. The normal range for plasma K values varied from 11 to 30.6 mg. %, average 20.2. Following operation, the blood K values were subject to a greater variation than during the control period but maximum concs. did not differ markedly from maximum control values. Hyperpotassemia cannot be considered as a contributing factor to collapse in exptl. intestinal obstruction in the dog.—Authors (Courtesy of Biol. Abst.).

BATE, JOHN T.: *Appendicitis Induced by Trauma.* Am. J. of Surgery, 48:437, May, 1940.

Bate does not believe that trauma is a factor in producing acute appendicular obstruction and cites evidence from the literature for and against this view.—Dwight L. Wilbur.

# Congenital Diaphragmatic Hernia

## Report of a Successfully Operated Case

By

JOHN H. WILLARD, M.D.\*

PHILADELPHIA, PENNSYLVANIA

**S**UCCESSFUL surgical repair of diaphragmatic hernias in childhood is no longer a curiosity. Truesdale in 1935 collected reports of 24 successfully operated cases and added four more of his own. An analysis of these reported cases, however, shows that a large proportion were traumatic in origin. It appears that successfully operated true congenital hernias are of sufficient rarity to warrant this report.

Z. S., a Jewish boy, aged 12 years, was first seen in June, 1939, because of recurrent attacks of nausea and vomiting over a period of 3 years. These attacks had been irregular in occurrence, sometimes daily for several days, or as isolated attacks with remissions of several weeks. Most attacks occurred between 10 and 12 p. m. and were preceded by a feeling of generalized abdominal fullness. Vomiting was profuse and often contained food retained for more than 12 hours. Emesis produced complete relief for several hours or several days. Constipation was present, being more marked during the periods when vomiting was frequent. For two weeks vomiting spells had occurred every 48 hours.

Delivery had been normal, and in infancy no digestive symptoms had been present. At the age of 3 years there was an attack of prolonged cough, fever and weight loss which had been diagnosed as pleurisy and bronchitis. For the next 5 years attacks of bronchitis were frequent. At this time studies were made in another hospital and a diagnosis of cystic disease of the lung was made. A needle was introduced into the chest but fortunately produced a "dry tap."

Physical examination showed a boy of normal height for his age but markedly underweight (77 pounds). His mental development appeared above normal. The chest was of the long flat type with definitely decreased expansion on the left. There was no flare of the ribs on inspiration (Hoover's sign). The right diaphragm was normal in position and movement but the left could not be definitely located because of a tympanic percussion note which extended from the third down to the twelfth rib. Breath sounds were normal in the right lung but were absent in the left. Peristaltic sounds were heard at the left base. The heart was displaced to the right, the right border being in the right mid-clavicular line. The abdomen was unusually scaphoid, although a succussion splash could be elicited down to the umbilical level and the descending colon was palpable. No other organs were felt.

Laboratory examinations included a normal blood count and urinalysis and a negative Wassermann. A fractional gastric analysis gave normal acid figures but showed delayed emptying.

X-ray study by Dr. J. D. Zulick demonstrated herniation of all the small bowel and most of the colon into the left chest with displacement of the heart to the right. The stomach was somewhat ptotic and dilated with definite dilatation of the duodenal cap. There was about 15 per cent gastric retention of the barium meal 6 hours later at which time the terminal small bowel and colon were filled

with barium. Barium enema showed all of the colon except the descending and sigmoid portions to be in the chest. The appendix was in the thorax. Because of the large size of the hernia it was thought that this might represent a case of congenital absence of the left diaphragm. Lateral films, however, showed the loops to be posterior and suggested shelving at the level of the diaphragm anteriorly.

In an effort to control the symptoms which apparently were due largely to duodenal obstruction from torsion of the duodenum, the boy was hospitalized and placed on an hourly feeding program. Daily gastric extractions showed progressively less gastric residue but on increasing the diet retention again appeared. It was felt that, since medical therapy had little to offer and intestinal obstruction was a constant possibility, surgery should be attempted.

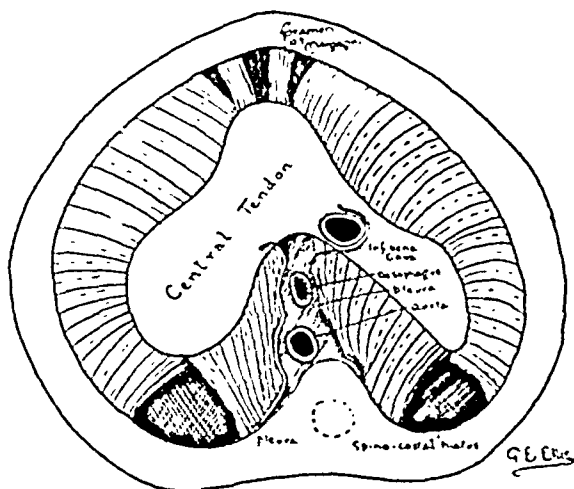


Fig. 1. Sketch of diaphragm showing location of Foramen of Bochdalek (Spino-costal hiatus) (Dunhill) (9).

Dr. Damon B. Pfeiffer performed the operation August 4, 1939, using an abdominal approach. Intra-tracheal ether anesthesia was given. Only the liver, stomach and distal colon remained in the abdomen; the entire small bowel, proximal colon and spleen being in the thorax. The duodenum was sharply angulated in the descending portion. The hernial orifice was postero-lateral and measured about 10 cm. in diameter. Adhesions were absent, allowing prompt reduction of the hernia without difficulty. There was no sac. The left lung was completely collapsed. In spite of an intact phrenic nerve the diaphragm itself was flaccid. Repair was accomplished without too great difficulty although the lack of any portion of the postero-lateral leaflet necessitated suturing to the intercostal muscles. One of the most troublesome features was introducing the viscera into the small abdominal cavity for the first time. This was finally accomplished by completely

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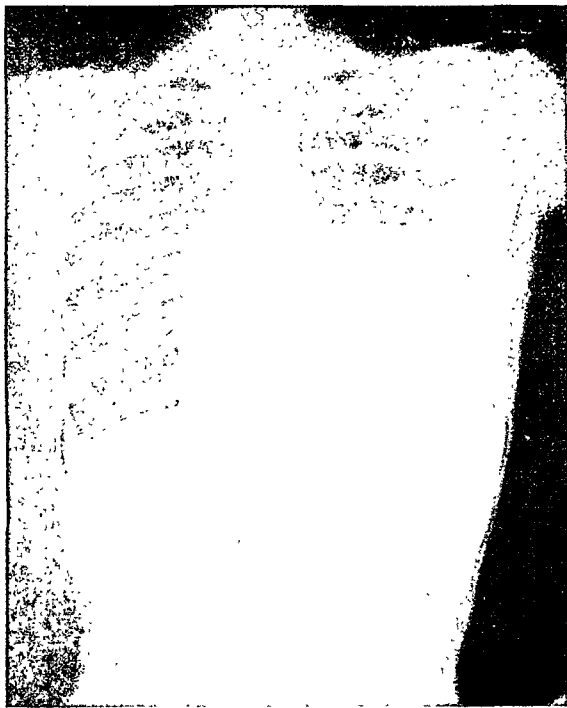


Fig. 2. Air filled bowel loops in chest; heart displaced to right.

emptying the stomach and bowel by means of gastric and rectal tubes.

Postoperatively the course was surprisingly smooth. Oral feedings were not started until the 5th day, continuous gastric drainage being used up to this time. On the 3rd day a left hydrothorax was demonstrated. A bed-side chest plate at this time showed slight expansion of the left lung with a large effusion. Three weeks later the lung was 40 per cent expanded and the effusion less. The patient was discharged August 31, 1939, in satisfactory condition.

X-ray studies three weeks later showed complete expansion of the lung with return of the heart to the left side. A small effusion persisted. There were no symptoms on a liberal bland diet and there had been a weight gain of 6 pounds over the preoperative level.

A further study was done one month later (10 weeks post-operatively). At this time there was only a slight suggestion of effusion. Gastric X-ray examination showed the stomach displaced to the right but emptying was normal. Unfortunately a complete small bowel and colon study was not done.

On last report (5/13/40) ten months post-operative, there were no symptoms and the weight was 110 pounds, a gain of 35 pounds since hospitalization.

DISCUSSION

(1) *Types of Hernia:* Diaphragmatic hernias are usually classified as traumatic or non-traumatic. The latter may be congenital or acquired. Harrington lists the *congenital* sites in order of their occurrence: (1) Hiatus pleuroperitonealis (Foramen of Bochdalek); (2) dome; (3) esophageal hiatus; (4) Foramen of Morgagni (post-sternal or parasternal); (5) absence of a portion or entire half of the diaphragm. *Acquired* hernias occur post-natally through one of the above mentioned sites or through a faulty embryonic fusion point. Most of these lesions are on the left side. The

TABLE I

Site	Cases	Content	Cases
Esophageal hiatus	153	Stomach Stomach, omentum, spleen Stomach and colon	144 3 6
Short esophagus	11	Stomach only	11
Foramen of Bochdalek	4	Colon and small intestine Stomach, small intestine, colon and spleen	3 1
Absence of posterior 1/4 left diaphragm	4	Stomach, small intestine, colon and spleen Small intestine and colon	3 1
Foramen of Morgagni	2	Colon and omentum	2
Left dome (trauma 31) (inflammatory 4)	35		35
Right dome (trauma)	1		1
	210		210

relative frequency of symptoms requiring surgical attack in the various types of hernia in all age groups is indicated in Harrington's figures of operated cases (5) (Table I).

It will be noted that esophageal hiatus and traumatic hernias comprise the largest groups of operated cases in this series. True congenital lesions represent only about 10 per cent.

Abdominal viscera may be involved in the hernia in various combinations. In this series, as in others, the stomach is not commonly involved in lesions of the Bochdalek type.



Fig. 3. Six hours after barium meal.



Fig. 4. Twenty-four hours after barium meal.

(2) *Embryology:* Various writers have reviewed the embryology of the diaphragm in explaining the location of these hernias (6, 9). The ventral portion of the diaphragm is formed by the septum transversum which lies between the heart and the abdominal viscera in the young embryo. It is first located in the neck but by the third month is at the level of the 12th dorsal vertebra. Here it is joined by a thickening of the mesodermal cells at the upper end of the dorsal mesentery. Until the end of the second fetal month a postero-lateral communication remains between the peritoneal and pleural cavities, the so-called pleuro-peritoneal canal or Foramen of Bochdalek. In the third month the foramen is closed by layers of pleura and peritoneum. Hernias occurring before closure have no sac while those developing after the second fetal month will have a sac. Similar hernias may occur through spaces left by faulty closure of the diaphragm in the retrosternal area (Foramen of Morgagni) or due to absence of the posterior portion of one leaf of the diaphragm. Most congenital hernias are on the left side, possibly because there is greater protection on the right side by the liver.

Acquired hernias may develop in these same locations due to imperfect closure, but most adult hernias occur through a relaxed esophageal hiatus or as the result of trauma.

Congenital anomalies such as thoracic stomach or short esophagus may produce similar symptoms and findings but are not classified as diaphragmatic hernias. Eventration of the diaphragm may also give a similar picture. This lesion does not represent a herniation through the diaphragm, but an abnormal elevation of the dome.

(3) *Incidence:* Previous to twenty years ago, diaphragmatic hernias were considered a rarity. Morrison

(2) in 1925 collected only seven cases of all ages from literature reporting 25,000 roentgenologic studies, but found 42 in 3,500 gastro-intestinal studies of his own. Pancoast and Boles (3) reported 16 cases found in 9,000 gastro-intestinal roentgen studies and stated that up to 1923 only 47 cases had been diagnosed during life. Most of these were in adults and were of the esophageal hiatus type. Recent reports show a higher incidence probably because of improved X-ray technique. At the Cleveland Clinic 31 cases were found in 2,213 examinations reported in 1938 (4). Harrington (5) states that at the Mayo Clinic a diagnosis of diaphragmatic hernia was made in 514 cases between the years 1908 and 1938. Only 20 of these were diagnosed prior to 1924. This author operated on 210 cases of all ages between the years 1926 and 1938. There is a growing literature reporting diaphragmatic lesions in infants and children. Congenital hernias were formerly believed to be beyond surgical help. Keith (6) in 1924 collected 21 cases, two-thirds of which died at or before birth; only two lived longer than a few weeks. Hedblom (7) in a large series found that one-third of the children died before reaching one month. Truesdale (1) collected from the literature 303 cases of all types of diaphragmatic hernia in children. One hundred and sixty-five were diagnosed at autopsy, 90 by X-ray, 35 clinically and 13 at operation. (There is no adequate statistical basis for calculating the actual percentage incidence in children).

(4) *Symptoms and Diagnosis:* Because of the variety of organs involved and the variable extent of disturbance in cardiac, pulmonary and digestive functions, the symptoms of diaphragmatic hernia are protean. In children with congenital lesions the most



Fig. 5. Barium enema.

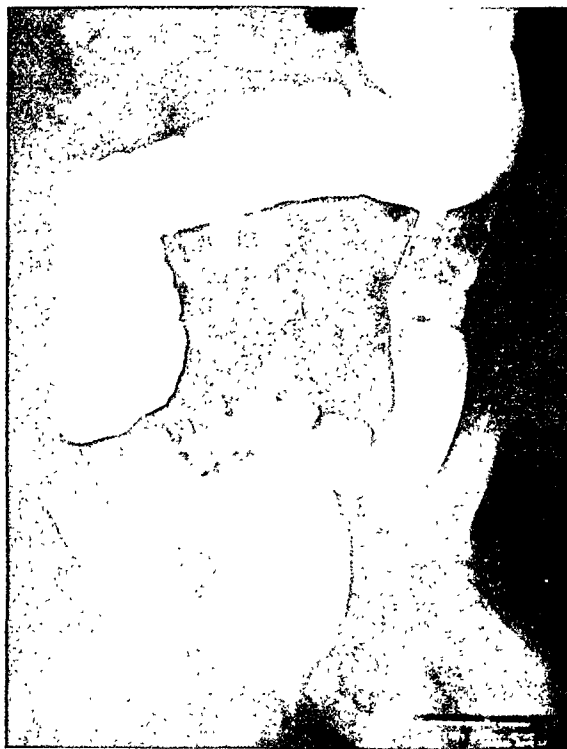


Fig. 6. Position of colon eleven months after operation.

common cause of death is intestinal obstruction. Pulmonary symptoms are often the earliest indication of a diaphragmatic disorder and chronic bronchitis or pneumothorax are frequently diagnosed. Displacement of the heart may cause circulatory embarrassment and some cases may first be thought to have dextrocardia. Several of the reported cases correspond to the one detailed above with duodenal obstruction due to torsion. At least one previous case had also been misdiagnosed as congenital cystic disease of the lung.

While the diagnosis may be suspected by the physical signs in the more extensive cases, X-ray study including a barium meal and barium enema is usually required. By careful study at different times and in various positions, the type of hernia may be shown. It is not uncommon, however, to find quite a different situation at operation than was indicated by X-ray study. Large hernias are difficult to distinguish from congenital absence of a portion or all of the leaflet, and evagination may be impossible of differentiation preoperatively in spite of careful X-ray study.

(5) *Treatment:* Since diaphragmatic hernias in children so frequently are associated with severe complications such as intestinal obstruction, pulmo-

nary and circulatory disturbances, there is a growing tendency to attempt surgical repair even at an early age. A survey of the literature reveals that a great proportion of the congenital cases do not survive the first year if repair is not attempted (6, 7, 10). Successful operations have been reported on infants aged 24 hours (11), 13 days (12) and 27 days (13) respectively. In 1935 Truesdale (1) collected reports of 44 operations in children with an operative mortality of 45 per cent. In his own series of 10 patients there had been only one death. Donovan operated on 6 of 10 children, all but one under 6 months of age. Four of the six were successful while two died. Two of the four non-operated cases died.

It is difficult to classify all of the reported cases but

TABLE II

*Successful operations: Foramen of Bochdalek hernias*

Year	Author	Age of Patient
1926	Truesdale (15)	6 years
1927	Jowers (16)	7 years
1929	McFadden (17)	4 years
1931	Truesdale (15)	1½ years
1931	Truesdale (15)	12 years
1931	Donovan (18)	4 months
1931	Robb (19)	4 weeks
1931	Coryllos (12)	13 days
1935	Weinberg, Hamilton (20)	5 months
1938	Donovan (21)	6 months
1938	Donovan (21)	5 months
1939	Morton (22)	5 months
1939	Harrington (5)	4 Cases. Ages not stated

Table II lists those apparently of the Foramen of Bochdalek type which have been successfully operated as reported in English.

### SUMMARY

(1) Congenital diaphragmatic hernias in children are of serious prognostic significance. (2) Successful surgical repair may be accomplished even in young infants. (3) A case of successful repair of one type of congenital hernia, through the Foramen of Bochdalek, in a boy 12 years is reported. (4) Only 16 similar cases in children under 15 years of age could be found in the literature.

I wish to acknowledge the cooperation of Dr. Damon B. Pfeiffer, Director of the Surgical Service, Abington Memorial Hospital, without whose surgical skill this successful case could not be reported and Dr. J. Donald Zulick, Director of the X-ray Department, Abington Memorial Hospital, whose careful examinations were valuable aids.

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# I. An Experimental Study of the Effect of the Pituitary on the Motility of the Gastro-Intestinal Tract

## A Preliminary Report\*

By

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and

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AT the last meeting of this Association we reported some studies on the effect of the thyroid on gastro-intestinal motility. In that communication (1) we recorded the acceleration of motility produced by thyroid medication in both normal and vagotomized dogs. We also pointed out that bilateral thyroidectomy had no immediate effect upon motility. Combined effects of vagotomy and thyroidectomy were the same as those of vagotomy alone and could be overcome by thyroid medication. This led us to believe that the effect of thyroid medication was independent of vagus continuity but later we found (2) that atropinization could annul this effect.

It seemed opportune to utilize this same group of dogs, which we had observed repeatedly and therefore knew well so far as their responses were concerned, for a study of the action of the pituitary. There was also the thought that since the anterior lobe of the pituitary gland elaborates a thyrotropic principle, among several others, it might be possible to evaluate its action. As will be seen, the problem became so complex that we are reporting only certain phases of it at this time, even excluding studies on dogs with hypophysectomy alone, since so much of the work is still in progress and a more complete summary is intended later.

Cushing (3), in 1912, was among the first to show that total hypophysectomy in dogs was followed by rapid involution of the thyroid and yet contrary to current opinion the relationship of the anterior lobe of the pituitary to the thyroid gland has not been extensively studied in man. In recent years, however, many investigators (4) have demonstrated that the anterior lobe of the pituitary contains a hormone which stimulates the thyroid gland. Nevertheless, the knowledge of hormones of the anterior lobe of the pituitary is as yet quite incomplete. Although a variety of fractions with supposedly specific functions have been prepared, much of their chemical natures is quite uncertain and their therapeutic uses, except in a few conditions, are still largely dependent on animal rather than clinical investigation. With reference to the digestive tract Collip (5) believes that the pituitary hormones are not essential for its functioning and this, he observes, is shown by the failure of hypophysectomy to produce any well defined changes in

digestive functions, an opinion which some believe is open to discussion. Such controversial opinions are partly responsible for the present investigation.

The present study of the effect of the pituitary upon the motility of the gastro-intestinal tract is limited to the following group of observations:

A. The effect of the administration of anterior lobe pituitary extract upon the gastro-intestinal motility:

1. Of normal dogs.
2. Of the vagotomized-hypophysectomized dog.
3. Of vagotomized-thyroidectomized-hypophysectomized dogs.
4. Of the thyroidectomized-hypophysectomized dog.
- B. The effect of the operations themselves:
  1. Upon motility of the gastro-intestinal tract.
  2. Upon gastric secretion.

In other words, we have simply superimposed the operation of hypophysectomy and the treatment with anterior pituitary lobe extract upon a group of standardized dogs.

In four normal dogs (average weight 8 kgs. each), anterior lobe pituitary extract was injected to a dosage of 30 cc. over a period of 20 days. X-ray studies were made to determine the effect of such treatment on the motility of the gastro-intestinal tract.

It was found on repeated examinations that the stomach was completely empty in six hours and that the head of the barium meal was in the descending colon. In a series of eight dogs in which normal gastro-intestinal motility was studied, precisely the same findings were observed. It therefore follows that anterior pituitary lobe extract has no demonstrable or significant effect upon gastro-intestinal motility in the normal dog.

The vagotomized dog was hypophysectomized and after a three week recuperative period X-ray studies of the gastro-intestinal tract revealed a gastric retention with the barium scattered through both the small and large intestines. This picture exactly duplicated that of the animal after bilateral vagotomy alone. Six weeks after the pituitary operation a similar X-ray picture was observed. This dog was placed upon anterior lobe pituitary treatment for a period of three weeks. For one week the dog was given oral pituitary therapy (pituitary body anterior lobe, desiccated) in a dosage of  $\frac{1}{2}$  gram daily and for two additional weeks increasing dosage of the extract was administered subcutaneously to a total dose of 21 cc.

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Presented before the American Gastro-Enterological Association, Atlantic City, June 10, 1940.



A six hour X-ray study made at this time revealed a gastric retention with the head of the barium meal in the distal colon. The latter picture did not differ significantly from that observed without pituitary therapy and without hypophysectomy.

In the two vagotomized-thyroidectomized-hypophysectomized animals, roentgen studies made three weeks after the hypophysectomy revealed a gastric retention with most of the barium in the small intestines and a small amount in the large intestine. This X-ray picture was not significant since it usually results from the vagotomy alone. Five weeks after the pituitary operation there was still a large gastric retention with the barium scattered through both the small and large intestines. Increasing subcutaneous doses (to a total of 21 cc.) of anterior lobe pituitary extract were administered for two subsequent weeks to these two dogs. X-ray studies made at this time, i.e. a six hour examination, revealed a large gastric retention with most of the barium in the small bowel and a small amount of the colon. One dog was made ill by the pituitary treatment. The X-ray pictures in these two animals were similar to those observed in the animals which had a vagotomy alone.

In the remaining dog in which a thyroidectomy and later an hypophysectomy had been performed, several X-ray studies made prior to treatment showed in each instance a normal gastric emptying. Occasionally there was a small gastric residue, a variable finding, but the progress of the meal through the intestinal tract was normal. The administration of anterior lobe pituitary extract in the manner already described did not change this X-ray picture.

#### COMMENT

It has been reported by others and can be verified by any observer that hypophysectomy alone does not affect the motility of the gastro-intestinal tract. Though it must be admitted that in the presence of a vagotomy the effect of a superimposed hypophysectomy may not be apparent, the same cannot be said in the case of thyroidectomy. In the latter instance the effect of thyroidectomy is practically nil for clinically this dog had not developed myxedema and therefore any additional effect must be attributed to the hypophysectomy. However, the latter operation produced no demonstrable change in the roentgen-ray findings. Furthermore, the administration of adequate amounts of anterior pituitary lobe extract, orally or subcutaneously or both, unlike thyroid medication, did not in any degree, affect the motility of the gastro-intestinal tract either in the normal or in the variously operated

dogs. More complete studies now in progress seem to bear out this impression.

Gastric test meals (50 cc. of 7% alcohol) made upon this series of hypophysectomized animals without gland treatment are tabulated below:

Dog	Operation	Free HCl (One Hour Extractions)	Total Acidity
1	Vagotomy-hypophysectomy	50	74
2	Thyroidectomy-hypophysectomy	62	76
3	Vagotomy-thyroidectomy-hypophysectomy	38	56
4	Vagotomy-thyroidectomy-hypophysectomy	52	74

These values may be considered within normal limits.

In this connection it is interesting to recall the report of Snapper (6) who observed five patients with insufficiency of the anterior lobe of the pituitary body and found an associated complete gastric achylia. The suggestion is made that a possible physiologic effect of the anterior lobe on gastric secretion may be implied. On the other hand, Waterman (7) examined the gastric contents of 192 hypophysectomized rats, in 27 per cent of which the stomach was found to be empty and no acid juice was secreted. However, if the stomachs of these animals were filled with food, hydrochloric acid could always be demonstrated in the contents. Waterman concludes that although pituitary extracts may produce an increased gastric secretion, hypophysectomy is not necessarily followed by achylia gastrica in the animals mentioned.

#### CONCLUSIONS

Though they may be modified by the more or less indirect method of approach the following conclusions seem justifiable:

1. Gastro-intestinal motility in normal dogs is not affected by the subcutaneous administration of anterior lobe pituitary extract therapy.
2. Gastro-intestinal motility is not affected by hypophysectomy.
3. The administration of anterior lobe pituitary gland to these hypophysectomized animals had no effect upon gastro-intestinal motility.
4. Gastric test meals in these operated but otherwise untreated dogs revealed normal secretory values.

Note: The preparation of the pituitary materials used in these studies is discussed in the final note of Section 2.

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## II. An Experimental Study of the Effects of the Pituitary and Thyroid Glands on Carbohydrate Metabolism

### A Preliminary Report\*

By

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**I**N the same group of dogs utilized for the preceding study (Section I. See page 451) investigations were made on the effect of anterior lobe pituitary gland extract (anterior lobe pituitary body, see final note) and desiccated whole thyroid gland (U.S.P.) therapy upon sugar metabolism.

#### THE EFFECT OF ANTERIOR LOBE PITUITARY EXTRACT ON NORMAL DOGS

Blood sugar tolerance tests, following the administration of 100 grams of dextrose by stomach tube, were carried out on four normal dogs at the end of a 21 day period of daily subcutaneous injections of anterior lobe pituitary extract to a total dosage of 31 cc. The blood sugar values (determined by the Folin-Wu method) and the corresponding curves are presented in Chart 1.

From this chart it is seen that the animals have a decreased sugar tolerance with a diabetic type of curve, illustrating the diabetogenic (hyperglycemic) effect of this anterior lobe pituitary extract on the normal dog. These findings are in accord with those obtained by Houssay (1) and others (2, 3) who have shown that anterior lobe pituitary extract can produce diabetes in normal mammals. In discussing the diabetogenic action of anterior pituitary lobe extract Houssay reports that in the dog the blood sugar begins to rise gradually from the second or third day of injection until it reaches levels of 0.18 to 0.30 per cent.

#### HYPOPHYSECTOMIZED DOGS — "PLUS"§

In two hypophysectomized-vagotomized dogs, one with and one without thyroidectomy, in which no medication was given, blood sugar tolerance tests yielded the data presented in Chart 2.

These findings indicate an increased tolerance and increased mobilization with a hypoglycemic tendency. Since they are based on only two animals no definite conclusions can be drawn, but further work is in progress on this phase of the problem. The observation has been established that in the absence of the pituitary gland there is a tendency to hypoglycemia and hypersensitivity to insulin. Moreover, hypophysectomized dogs rapidly develop hypoglycemia when fasted (5).

It has also been found that larger doses of sugar by

mouth or glucose by injection were necessary to produce glycosuria in hypophysectomized than in normal dogs, although this increase in tolerance was not confirmed by all investigators.

In dogs, Houssay observed that 2 grams of glucose administered by mouth per kilo of body weight produced in the normal a sugar curve which rises higher and descends lower while in the hypophysectomized animal the curve rises lower and descends more gradually although there are some variations, such as our work demonstrates. After the intravenous administration of 1 gram of glucose per kilo the sugar curve in the hypophysectomized dog rises higher and descends more slowly. On the other hand, if hypophysectomized rabbits receive glucose by mouth the blood sugar rises less and the secondary fall in blood sugar is greater than in normal rabbits.

It has already been demonstrated by us (4) that vagotomy alone does not significantly influence carbohydrate metabolism. Houssay has also reported that the vagus has only a secondary and accessory role causing a more rapid and perfect regulation in these cases. After section of the vagus nerves, for example, it was found that the blood sugar is maintained within normal limits and the curve of sugar tolerance is only slightly affected.

#### ANTERIOR LOBE PITUITARY EXTRACT THERAPY IN HYPOPHYSECTOMIZED DOGS — "PLUS"

Blood sugar tolerance tests were carried out in three hypophysectomized dogs with and without thyroidectomy; each had two weeks of subcutaneous treatment (total dosage 21 cc.) with anterior lobe pituitary extract. The results are presented in Chart 3.

In this chart one observes relatively normal curves and it appears that in the absence of the pituitary gland the medication acts as replacement therapy.

#### EFFECT OF THYROID THERAPY ON CARBOHYDRATE METABOLISM

It was of interest to observe what effect thyroid therapy would have upon the normal dog and upon those which have been thyroidectomized-hypophysectomized. Desiccated whole thyroid gland (U.S.P.) was administered daily by mouth in a dosage of 0.4 gm. per kilo body-weight.

#### THE EFFECT OF THYROID THERAPY ON NORMAL DOGS

In four normal dogs sugar tolerance tests were done. One had no thyroid therapy and three had thyroid

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§"Plus" refers to the other operations.

Presented before the American Gastro-Enterological Association, Atlantic City, June 10, 1940.

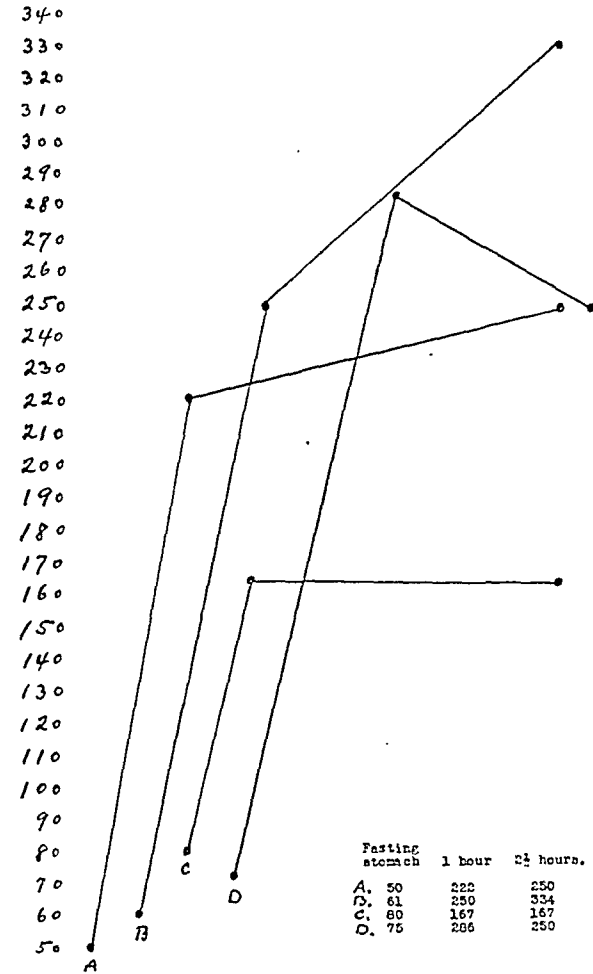


Chart 1. Blood sugar tolerance curves on four normal dogs showing the diabetogenic hyperglycemic effect produced by the subcutaneous administration of the extract of anterior lobe of the pituitary gland.

treatment for a period of 18 days. The results are presented in Chart 4. These values indicate that thyroid therapy produces a thyroid hyperglycemia effect. It has been reported by others (1) that thyroid treatment increases the resistance of normal or thyroidectomized animals to insulin but decreases it if given in excessive doses.

THYROID THERAPY IN HYPOPHYSECTOMIZED DOGS—"PLUS"

In three hypophysectomized dogs, with and without thyroidectomy, similar thyroid therapy over a period of 18 days yielded the results shown in Chart 5. These values indicate that the effect of thyroid therapy in the absence of the pituitary or thyroid glands or both differs markedly from that which occurs in the normal following thyroid medication. The striking hyperglycemic curve which was observed in the normal is no longer present. Similar observations were made in these same animals following the administration of anterior lobe pituitary extract. In each case therapeutic administration of either anterior pituitary or thyroid extract overcomes the effect of the gland removed (i.e. acts as replacement therapy) and allows the latent hypoglycemic effect of

the remaining glandular deficiency to assert itself. In other words, by therapy we actually produce the same effect on the blood sugar as would follow the replacement of the gland itself. It would seem that with regard to carbohydrate metabolism anterior pituitary gland and thyroid gland medications are not medicated through either gland necessarily because in two instances both have been removed. Furthermore, Long, Katzin and Fry (6) report experiments on the diabetogenic effect of anterior pituitary extract in adrenalectomized-pancreatized animals which indicate that such activity is not mediated entirely by the adrenal cortex but that a synergism between the two hormones may explain the mechanism. On the other hand, Houssay believes that the so-called diabetogenic hormone has a direct action independent of its influence on the thyroid or adrenals although its effectiveness, like that of other agents, is less or may even fail in profound adrenal insufficiency. The direct action is to stimulate and facilitate the production of sugar and perhaps to regulate its utilization. In other words, the anterior lobe of the pituitary has a glucose regulating effect.

BASAL METABOLISM

In the three hypophysectomized dogs, one vagotomized, one thyroidectomized and one vagotomized-thyroidectomized, basal metabolism tests carried out by Dr. D. C. Smith, yielded the following results:

Dog	O <sub>2</sub> consumed per min. per kg.	R.Q.
1	4.4	.84
2	4.8	.80
4	3.4	.81

	Fasting stomach	1 hour	2 1/2 hours
A.	75	167	87
B.	61	100	61

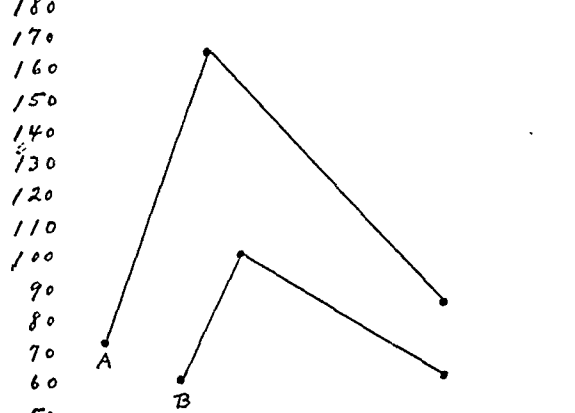


Chart 2. Blood sugar tolerance curves on two untreated hypophysectomized-vagotomized dogs, and (A) with thyroidectomy and one (B) without thyroidectomy showing a hypoglycemia.

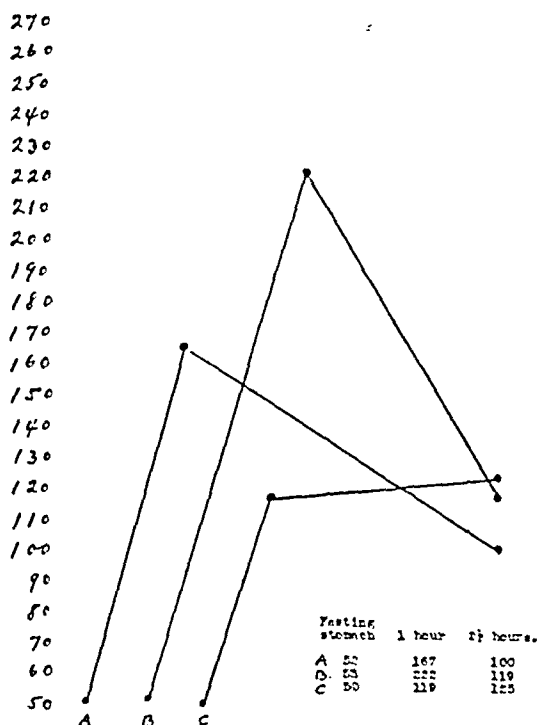


Chart 3. Blood sugar tolerance curves on three hypophysectomized dogs one (A) with vagotomy, one (B) with thyroidectomy and one (C) with thyroidectomy and vagotomy. They illustrate the relatively normal curves produced by the subcutaneous injections of extract of anterior lobe pituitary body under such conditions.

These values correspond to those obtained in thyroidectomized animals with low basals. It is of interest in this connection to call attention to the report of Verzar and Wahl (7) who showed that anterior pituitary extract raised the basal metabolic rate of guinea pigs with intact thyroids, but that following total thyroidectomy, pituitary extract had no effect on metabolism. Houssay has recorded the observation that in dogs the action of the anterior pituitary on basal metabolism is essentially through the thyroid and that hypophysectomy causes an atrophy of the thyroid epithelium and provokes hypothyroidism with lowering of the metabolism. Moreover, hypophysectomized dogs apparently do not have a raised consumption of sugar since their basal metabolism is slightly diminished and the R.Q. is normal.

#### COMMENT

It is striking to observe the intimate relationship between the effect of thyroid gland and anterior pituitary gland therapy on carbohydrate metabolism in the normal as well as in the hypophysectomized-thyroidectomized animals. The duplication of thyroid action and pituitary action in these studies has not been stressed by others except for the demonstration that whereas excessive pituitary action produces diabetes the same action on the part of the thyroid produces only hyperglycemia. Our experiments seem to indicate that the action on carbohydrate metabolism of either thyroid or anterior pituitary is not mediated through either gland alone. This is in contrast to the mediation of the pituitary effect through the thyroid

in the case of basal metabolic rate. Such work is informative because it is not complicated by the removal of the pancreas, an operation which forms the basis of so many reports in this field.

#### CONCLUSIONS

1. The administration of anterior lobe pituitary extract to the normal dog produces a hyperglycemic (diabetogenic) effect.
2. Sugar tolerance tests in hypophysectomized dogs with and without thyroidectomy, reveal an increased tolerance or hypoglycemic effect.
3. Sugar tolerance tests in hypophysectomized dogs with and without thyroidectomy to whom anterior lobe pituitary extract had been administered show relatively normal curves.
4. The effect of thyroid therapy upon the blood sugar of normal dogs is to produce a hyperglycemia.
5. Thyroid therapy in hypophysectomized dogs with and without thyroidectomy, produces an effect approximating a normal curve.

Note: Autopsies were performed on the hypophysectomized dogs by Dr. L. Freedom. Gross inspection at autopsy verified the total removal of the pituitary gland. Microscopic studies are being pursued and will be reported subsequently. The hypophysectomies were done by Dr. W. B. Scoville to whom we are indebted.

N. B.: The desiccated anterior lobe pituitary body used in these studies is the carefully desiccated material meeting the requirements of the National Formulary. The anterior pituitary extract is a water soluble extract of the anterior lobe of the pituitary gland. No standardization is claimed for the latter product in terms of unit values of specific hormones.

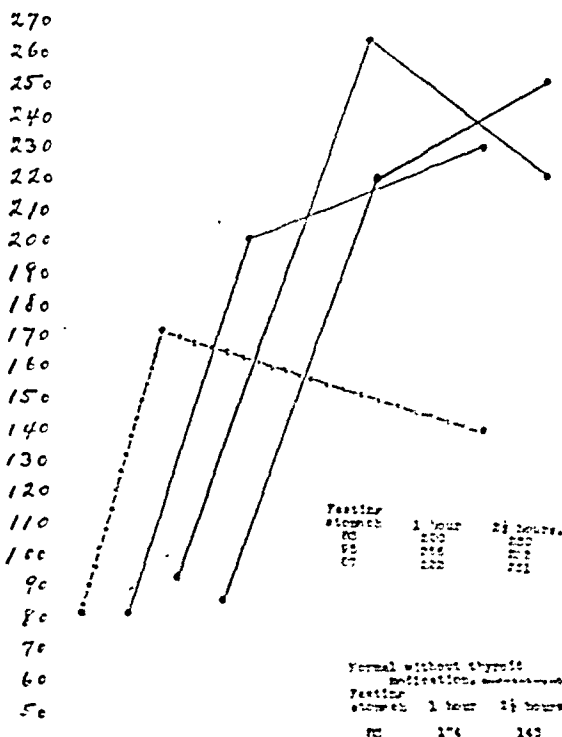


Chart 4. Blood sugar tolerance curves in four normal dogs, three of which were treated with thyroid. Note the hyperglycemic effect.

However, for our subsequent studies we have made arrangements for the preparation of a definitely standardized anterior pituitary product.

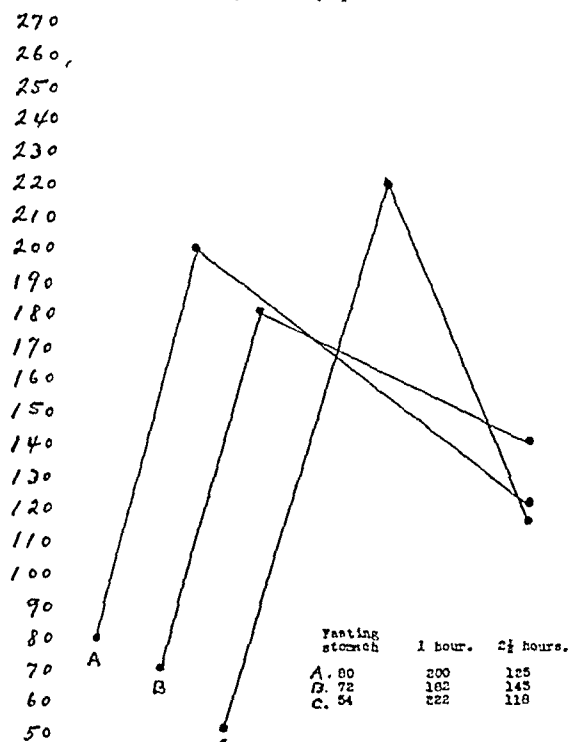


Chart 5. Blood sugar tolerance curves after thyroid treatment on three hypophysectomized dogs: (A) with thyroidectomy, (B) with thyroidectomy and vagotomy and (C) with vagotomy showing curves approximating the normal.

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## DISCUSSION

DR. JULIUS FRIEDENWALD (Baltimore): Mr. President: In their presentation last year Drs. Morrison and Feldman presented experimental evidence to indicate that increased thyroid activity increased gastro-intestinal motility. At that time I suggested that this problem was far from simple since the thyroid rarely functioned alone and that further studies were necessary to clarify the role played by various glands on gastro-intestinal function.

In their more recent study the problem concerned itself with the effect of the pituitary on the motility of the gastro-intestinal tract. Unlike the thyroid, the gastro-intestinal motility does not appear to be affected by the administration of anterior pituitary extract. On the other hand, the administration of anterior lobe pituitary extract was found to bring about a hyperglycemic state in normal dogs, whereas hypophysectomy was followed by a hypoglycemia.

The close relationship of certain of the endocrines to the digestive systems is still obscure in many respects. It is to be hoped that further studies of these problems may more clearly define the relationship that exists between the gastro-intestinal endocrine systems.

## The Fate of Ingested Glucose Solutions of Various Concentrations at Different Levels of the Small Intestine\*

By

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RECENTLY we (1) reported on the behavior of various concentrations of glucose in the gastro-duodenal segment. In the past year we have extended our studies to the other segments of the small intestine.

### EXPERIMENTAL DATA

Our experimental technic was essentially that previously reported (1). However, instead of the three-lumen tube, a four-lumen tube was used. This tube was constructed for us on our specifications by George P. Pilling and Son. Through lumen 1, at the distal end, a balloon was inflated; above this a distance of 3" with holes  $\frac{1}{2}$ " apart opened into lumen 2; above these holes, a second balloon connected to lumen 3; and finally, a distance of 3" with holes  $\frac{1}{2}$ " apart opening into lumen 4. (Diagram I).

\*From the Medical Research Laboratory Samuel S. Fels Fund, and the Gastro-Intestinal Division Medical Service I, Mt. Sinai Hospital. Presented before the American Gastro-Enterological Association, Atlantic City, N. J., June 10, 1940.

This arrangement reduced failures from seepage past the balloon connected to lumen 3, since this material was retained by the distal balloon and collected through the openings in the segment between the balloons.

This precaution of an additional balloon and the collection of material are essential in any quantitative intestinal studies done in man. While a single balloon may be sufficient at times, we have seen repeatedly, by using the phenol red indicator, that slight seepage beyond a single balloon occurs very often.

In use, suction was applied to lumina 2 and 4 by means of a differential water level of about 70 cm. and a mercury manometer inserted in the circuit to make certain that the suction was constant. After partial inflation, the balloon lumina were connected to a constant-level device similar to that described by Abbott, Karr and Miller (2). This permitted flexibility in balloon-volume in response to peristaltic contractions while insuring constant balloon-contact with the intestinal walls.

The method of intubation was the same as previously described (1). When the intestinal tube was in the desired position and taped at the mouth, a Rehfuess tube was swallowed by the patient to approximately the 65 cm. mark. The two balloons were connected to the constant-level device and the balloon pressure adjusted to correspond to about 35 cm. of water. The pressure actually used varied above and below this as we tried to bring it to a point which would produce the maximum fluctuations in water level due to peristaltic contractions, because then

sample retained as previously described (1). The collection through the intestinal tube was also fractionated into 30 minute samples. This procedure continued until the stomach was empty, with intestinal drainage continued for a further 30 minute period. In this study lavages following final drainage from the intestine were eliminated as data previously obtained showed that the glucose and phenol red recovered were considerably less than the errors inherent in this type of study.

The stomach and duodenal samples were analyzed for

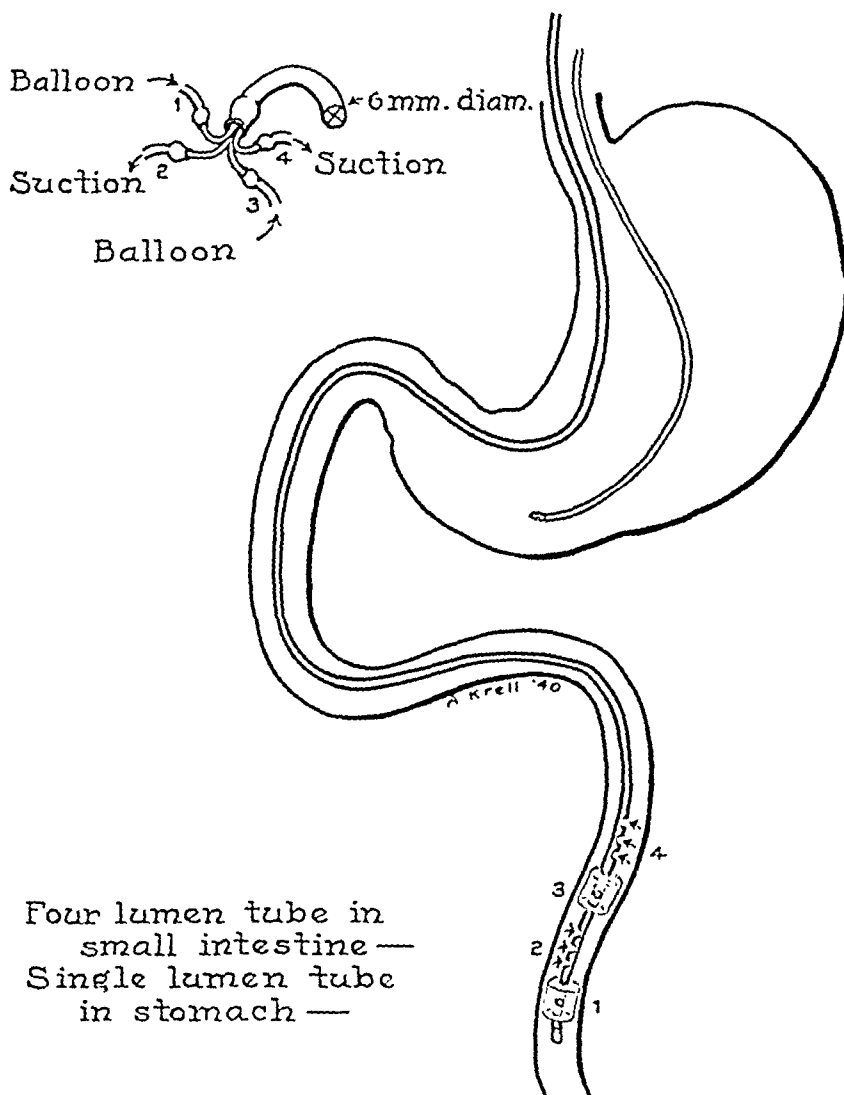


Diagram 1

the intestine is subject to the least amount of irritation from the balloons. At the same time, the balloons are sufficiently inflated to minimize the possibility of leakage of material. The amount of pressure required to achieve this effect varied in different patients and in the same patient differed from one intestinal level to another.

Lumina 2 and 4 were connected to flasks to which suction was applied and a fasting sample collected for 15 minutes. The flasks were then changed and the glucose meal given through the gastric tube. The stomach was emptied every 30 minutes, the volume measured, and a

glucose and chloride as previously described (1). Phenol red was determined by a modification of the Hollander method (2).

In addition to studying the absorption of glucose by the intestine, we followed the effect of this absorption on the blood glucose. This was done by determining blood glucose on capillary blood by a modification of the Folin Wu method.<sup>4</sup>

Studies were made with the tube at various levels in

<sup>4</sup>This method will be published at a later date.

the intestinal tract; namely, the duodenal jejunal junction, and with 3', 5' and 7' of tubing beyond the pylorus. These three latter positions were approximately the upper jejunum, lower jejunum, and ileum. (Since the intestine tends to creep up on the tube during the course of the experiment, these positions must be considered only approximate. In one experiment lasting some six hours the tube ultimately passed into the colon when only five feet of tubing were past the pylorus. This was confirmed by both the recovery of fecal matter and X-ray). The position of the intestinal tube was determined in most instances by X-ray before the instillation of the gastric meal and at the end of the experiment. The concentrations of glucose studied were 5.4%, 13.5% and 25%. While considerable effort and time were expended in attempting the same studies with 40% glucose, we were not sufficiently satisfied with the reproducibility of our results at the lower intestinal levels to justify their inclusion in this report. We are convinced that glucose solutions of such high concentration are undesirable even when placed in the stomach and have a distinctly irritant effect on the upper duodenum even though the stomach empties such a solution very slowly. Evidence of such an irritant action is our observation in many normal individuals of pyloro-

ported (1), we saw the remarkable versatility of the duodenum in shifting from an organ of glucose absorption to one of glucose dilution. One sees for example in the case illustrated in Table I, that with 250 cc. of 5.4% glucose instilled into the stomach during its passage through the duodenum 6.0 gms. of the total 13.5 gms. instilled were absorbed. The total volume of solution recovered at the lower end of the duodenum was 258 cc. as compared with 250 cc., the volume originally instilled. When the same volume of a 13.5% glucose was used under the same conditions, the total amount of glucose absorbed in its passage through the duodenum was greater (12.8 gms.) and the total volume recovered was 466 cc. With a similar meal of 25% glucose in the same patient, passage through the duodenum resulted in the absorption of essentially the same amount (10.9 gms.) as was absorbed with the 13.5% meal, and a volume recovery of 744 cc.

Well illustrated in Table I is the relationship of the duodenum to the absorption of glucose and water and

TABLE I

*The residual stomach volume, its dilution, and the recovery from the duodenum after gastric instillation of glucose meals of various concentrations.*

	Concentration of Glucose Meal Gm./100 cc.											
	5.4				13.5				25			
Time after instillation of meal (minutes)	30	60	90	120	30	60	90	120	30	60	90	120
Volume in stomach cc.	90	E			180	28	E		210	115	18	E
*Phenol red concentration mg./100 cc.	0.62				0.57	0.27			0.60	0.41	0.14	
Volume of original meal in stomach cc.	56				103	7			126	47	2	
Volume recovered from duodenum cc.	152	100	6		218	214	28	6	204	340	170	30
Total volume recovered from duodenum cc.	152	252	258		218	432	460	466	204	544	714	744
Glucose absorbed gm.		6.0				12.8				10.9		

\*Phenol red concentration of instilled meal = 1 mgm./100 cc.

spasm and failure of gastric emptying of a second 40% glucose meal given shortly after the first 40% meal has left the stomach. This confirms the duodenal irritation seen after highly concentrated glucose meals in the rat by Magee and Reid (4).

## RESULTS AND DISCUSSION

In this study we were able to confirm our previous results (5) on the relation of the glucose concentration instilled into the stomach to rate of gastric emptying. As the concentration of glucose increased above isotonicity to that degree gastric emptying was retarded. (Table I). We have shown that the amount of retardation is dependent upon the concentration of glucose reaching the duodenum, while, in the case of the operated stomach, upon the concentration of glucose reaching the jejunum (6)—results similar to those of Johnston and Ravdin (7) in dogs and of Ravdin, et al (8) in man. We have again been unable to find in man the striking speed with which water is drawn into the stomach by hypertonic glucose solutions as reported in the dog by Ravdin, Johnston and Morrison (9). In the case of the stomach and duodenum acting as a unit, again, as previously re-

of its essential function of dilution when hypertonic solutions reach it. While there was a larger amount of glucose absorbed after the 13.5% glucose meal as compared with the amount absorbed after the 5.4% meal, there was no increase in absorption after the 25% meal over that following the 13.5%. The maximum absorption rate was possibly reached with the 13.5% meal but the diluting mechanism is brought into still greater play by the 25% glucose meal.

The difference in behavior of the duodenum and the lower segments of the small intestine in respect to the interchange of fluid between lumen and blood is illustrated in Table II. When the glucose meals instilled are isotonic, no absorption of water occurs. With meals above isotonicity there is normally a flow of fluid from bowel wall into bowel lumen. However, at no point beyond the duodenum is there addition of fluid. Rather, there is a continuous absorption instead for the concentrations of meals studied. This does not mean that at these lower levels there would be no outpouring of fluid if solutions of the same concentration as reach the duodenum reached them. This would occur and has been shown in the results of Groen (10),

who instilled hypertonic solutions directly into the jejunum. Our results indicate to us that it is of questionable value to study the behavior of highly concentrated solutions instilled directly into the small intestine because, under normal conditions, the function of the pylorus and the resultant controlled gastric emptying coupled with the rapid influx of fluid into the duodenum prevent glucose concentrations of such intensity that would require further dilution.

Since absorption from jejunal loops increases with increasing concentration of glucose and since concen-

TABLE II

*The volume recovered at various intestinal levels after giving 250 cc. of glucose of various concentrations*

Recovery at Intestinal Level	Concentration of Meal		
	5.4%	13.5%	25%
Duodenum	258 cc.	465 cc.	744 cc.
Upper Jejunum	100 cc.	321 cc.	422 cc.
Lower Jejunum	82 cc.	276 cc.	325 cc.
Ileum	22 cc.	122 cc.	259 cc.

trated glucose solutions are prevented from reaching the jejunum when concentrated glucose meals are fed because of retarded gastric emptying and duodenal dilution, it is clear that gastric emptying is an important factor in determining sugar absorption. This was recognized by Adam (11) from his studies on infants and by Holtz and Schreiber (12) in their observations of the movement of sugar solutions, fluoroscopically, through the alimentary tract in dogs. Pierce (13) recognized that pyloric activity was an important factor in limiting glucose absorption.

In timing the first flow from the intestinal lumen following the instillation of the glucose into the stomach, we observed, as a rule, that the higher the glucose concentration instilled, the shorter the appearance time at the lower end of the duodenum. This is explicable because of two factors. First, there is a active duodenal peristalsis when hypertonic solutions reach the proximal duodenum. This factor, coupled with the inrush of diluting fluid (hence increased intestinal volume), explains the earlier appearance time of the glucose solutions at the lower duodenum after instillation of the more highly concentrated glucose meals. At the levels beyond the duodenum no such relationship of meal concentration and appearance time was found, this no doubt because beyond the duodenum concentrations of glucose at or below 5% were recovered even after the 25% glucose meals.

Table III shows the percentage of the total glucose absorbed at various levels. For isotonic glucose meals by far the greatest amount of the ingested glucose was absorbed by the duodenum and upper jejunum. After glucose meals of higher concentration these same portions of the small intestine absorbed only about half of the total glucose.

The changing function of the duodenum from absorption to dilution is again exemplified by the sharp drop in the percentage of the total amount of glucose absorbed as we changed from the 13.5% meal to the 25% meal.

After hypertonic glucose meals the percentage of

total amount of glucose absorbed beyond the duodenum was independent of the concentration and total amount of glucose in the gastric meal. This is not surprising if we realize that after hypertonic meals concentrations of glucose beyond the duodenum were always 5% or less.

If we remember that in an intact gastro-intestinal tract, the greater the concentration of the ingested meal, the larger the volume of isotonic or nearly isotonic glucose which reaches the jejunum by the time complete gastric emptying has occurred; if we remember further, that the rate of absorption for a given concentration of glucose in the intestine is constant, then with normal intestinal motility, the amount of glucose absorbed will depend upon the volume of a given glucose concentration that traverses the absorbing surface. Since absorption from the duodenum does not vary greatly after hypertonic glucose meals and since a nearly constant concentration is delivered to the major absorbing areas of the small intestine, regardless of the concentration of the gastric meal, it is clear why the proportion of the total of hypertonic glucose ingested that is absorbed at any intestinal level, is the same at the time when the complete meal has reached that level.

We believe that the rate of intestinal absorption of glucose is constant only for a given concentration of glucose and are in agreement with the findings of Ravdin, Johnston and Morrison (14) for the isolated jejunal loop in dogs, that the rate of absorption varies directly with the glucose concentration.

From our data we can now understand why Cori (15) was led to the conclusion that "the rate of absorption must be independent of both the absolute amount and the concentration of sugar present in the intestine, which means that neither an increase nor a decrease of these two factors can change the rate of absorption or that there is only one rate of absorption for each particular sugar." We must recall that Cori

TABLE III

*The amount of glucose absorbed at the different intestinal levels after gastric instillation of various concentrations of glucose*

Amount and Concentration of Glucose Meal	Amount and Per Cent of Total Glucose Absorbed			
	Duodenum	Upper Jejunum	Lower Jejunum	Ileum
13.5 gm. 5.4%	6.0 gm. 44%	10.9 gm. 81%	11.6 gm. 86%	13.1 gm. 97%
33.6 gm. 13.5%	12.5 gm. 37%	18.5 gm. 55%	24.5 gm. 72%	29.0 gm. 86%
62.5 gm. 25%	10.9 gm. 17%	35.9 gm. 57%	44.0 gm. 72%	52.4 gm. 84%

(15) carried out his investigations in rats by instilling concentrations of glucose ranging from 25% to 80% in the stomach. "The rats were sacrificed at hourly intervals after the sugar administration. The abdominal cavity was opened and ligatures were placed around the esophagus and the rectum. The stomach, small intestine, and the whole large intestine were carefully detached from the mesentery and placed in a beaker. The whole intestinal tract was cut open and the intestine washed out with successive portions of hot distilled water." We see thus that Cori in the first



place worked with hypertonic solutions only and, secondly, determined the glucose absorbed at fixed intervals from the complete gastro-intestinal tract. It is obvious from our segmental study of the small intestine that the varying concentrations, and hence varying total amounts of glucose which he placed in the stomach, produced a relative constancy of the amount of glucose absorbed per unit time that was only apparent and not real. Our explanation of the mechanism would be: the higher the concentration of the test meal, the slower the gastric emptying; a high degree of dilution and relatively little absorption of glucose by the duodenum; and the presentation to the more distal portions, the truly absorptive portions of the small intestine, of a stream of glucose that varied little in concentration, regardless of the concentration of the gastric meal. Then when the entire gastro-intestinal contents remaining at any given time were analyzed for unabsorbed glucose, the result led to an apparently constant absorption per unit time independent of the concentration and total amount of glucose in the gastric test meal. Ravdin, Johnston and Morrison (14) from their studies of glucose absorption on the isolated jejunal loops in dogs sensed the probable explanation for Cori's results when they wrote: "In fact, the concentrations found in the small bowel one hour after the introduction of a wide range of concentrations in the stomach, are of an order which, had these been placed in the isolated loop, no difference in the rate of absorption may have been demonstrable."

Ravdin, Johnston and Morrison (14) from their studies in the isolated jejunal loops in dogs found with increased concentrations of glucose increased amounts of absorption as well as increased absorption from increased volumes of the same concentration. They recognized that the use of the whole alimentary tract gives a more exact picture of what is happening in the organism as a whole. They believe, however, that their data would indicate what would happen when the jejunum or ileum is exposed to varying concentrations of glucose, such as would occur after gastro-enterostomy. When we consider, however, that in the resected stomach as well as after ordinary gastro-enterostomy, gastric emptying is delayed by hypertonic glucose meals in a way similar to that which occurs in the intact gastro-intestinal tract (6), it follows that in such operated states entrance of hypertonic glucose meals into the jejunum would be slow and intermittent. That the human jejunum can dilute is seen from the increased volumes obtained by Groen (10) in isolated intestinal segments after the introduction of various concentrations of glucose. On the basis of the motor behavior of the operated stomach with hypertonic solutions and the dilution mechanism which the jejunum apparently has, we are inclined to believe that in gastrojejunostomy, or after resection, that we would find a situation similar to that of the intact gastro-intestinal tract. Except that, as in the case of the motor function after operation, perhaps it would not be as efficient as in the intact tract. Studies in patients of this type are now under way. If, as we have seen, strongly hypertonic solutions of glucose are somewhat irritating to the duodenum, it is doubly important that such concentrated solutions be avoided after gastrojejunal anastomoses.

We should like to call attention to a concept that has gained favor concerning the concentration of glucose in the small intestine following various concentrations placed in the stomach. Ravdin, Johnston and Morrison (14) in studying this problem placed 200 cc. of a solution of glucose of varying concentrations into stomachs of healthy dogs after a 24-hours fasting period.

At the end of an hour the animals were rapidly anesthetized; the abdomen opened; a clamp put on the lower end of the esophagus, at the pylorus, and at the ileocecal junction. The contents of these sections; namely, gastric and entire small intestine, were collected separately and analyzed. In these experiments, one hour after the gastric introduction of 200 cc. of glucose varying in concentration from 10.4% to 50%, Ravdin, Johnston and Morrison (14) found concentrations of glucose in the entire intestinal contents varying in the small range from 2.4% to 5.3%. They believe that the changes in concentration of the glucose solution which remains in the stomach due to the rapid mobilization of water tend to bring the concentrations into a closer relationship within a period of only one hour and suggest that a longer period of time would probably result in an even closer equalization and conclude that because of this factor the variations in the concentrations of glucose solutions that reach the small intestine from the stomach are of a small order. These results have led to a feeling that the ingested sugar solution coming in contact with the intestine has approximately the same concentration irrespective of that of the original solution fed. This is true if one determines the concentration of glucose in the entire intestinal tract but such determinations do not indicate the much greater variations in glucose concentration to which the duodenum is subjected depending upon the concentration of glucose ingested.

Thus in Table IV for example, if we examine the results one hour after the gastric instillations of the

TABLE IV

*The glucose concentration of intestinal samples at the duodenum and upper jejunum after a meal of 250 cc. of various concentrations of glucose*

Concentration of Meal Gm./100 cc.	Concentration of Intestinal Samples in Gm./100 cc.			
	Duodenum		Upper Jejunum	
	30 Min.	60 Min.	30 Min.	60 Min.
5.4	3.1	2.7	2.5	
13.5	5.2	4.0	4.1	3.4
25.0	8.2	6.7	3.7	3.4
38.0	18.3	14.6		

same volume of different concentrations of glucose, we find that after a 5.4% meal, 2.7% glucose was recovered from the lower duodenum. After 13.5% gastric meal at the end of an hour, 4.0% at the same interval after a 25% glucose meal 6.7% were recovered and after a meal of 38.2% glucose, 14.6%. At the first half-hour recovery period, the range of concentration was even greater, being 3.1% for the 5.4% glucose meal, 5.2% for the 13.5%, 8.2% for the 25% meal, and 18.3% for the 38.2% meal. We see the increasing

concentration of glucose that may occur in the entire human duodenum after increased concentrations of the ingested meal. However, at the 3-foot mark the concentrations were 2.5%, 4.1% and 3.7% for the 5.4%, 13.5% and 25% meals respectively; thus at this level more closely paralleling the concentrations found for the entire small intestine of the dog by Ravdin and his associates (14).

### OSMOTIC RELATION IN THE INTESTINE

Osmotic pressures were calculated as previously described from the glucose and chloride concentrations (2Cl plus glucose). Although we did not determine bicarbonate values, the addition of the average bicarbonate figures reported by Abbott, Karr and Miller (2) for the various intestinal levels would not materially change our results.

At the lower duodenum as previously reported (1), the fasting contents were always somewhat hypotonic. Isotonicity was maintained after the 5.4% meal but with the higher concentrations hypertonic solutions were collected from the lower duodenum, the degree of hypertonicity varying with the concentration of the meal. Too, chloride concentration of the collected meal dropped after the gastric instillation of glucose and was lowest in those samples which had the greatest glucose concentration and increased as the concentration of glucose decreased.

Abbott, Karr and Miller (2) found that isotonicity was maintained below the duodenum and upper jejunum without regard to the various volumes and concentrations of solution of glucose ingested. We obtained similar results except for the lower ileum where we recovered solutions very definitely hypotonic even after 25% glucose meals placed in the stomach. At these levels we also saw, after the glucose meals, the reciprocal shift of chloride and glucose concentrations observed in the duodenum. In the jejunum and ileum the fasting contents were also hypotonic.

We (1) have seen that the duodenum absorbed water only from hypotonic solutions. From our present data we have seen too, that absorption of water in the jejunum and ileum also occurs from hypotonic solutions. That this is true for water absorption by the jejunum in the dog is seen in the results of Ravdin, Johnston and Morrison (14). Since we have observed the greatest degree of hypotonicity in the ileum, it indicates that the greatest water absorption would occur here.

### BLOOD SUGAR CURVES

The blood sugar curves resulting from the absorption of glucose depended naturally upon the quantity of glucose absorbed. The curves were strikingly similar after the absorption of similar quantities of glucose in the same individual and their form was related only to the amount absorbed and not to the level of the intestine to which the glucose had reached. The peak of the curve increased within certain limits, with an increase of the amount of glucose absorbed. The limit apparently was the quantity of absorbed glucose which fully stimulated the blood sugar reducing mechanisms. When this limit was reached, the peak of the blood sugar curve remained independent of any further increase in glucose absorption, results similar to those originally reported by Hansen (16) after varying the dose of glucose by mouth. However, the spread of the curve was much greater after the

meals of higher concentration. There are again applicable on the basis of our findings of the stream of glucose of relatively constant concentration which reaches the jejunum and ileum after hypertonic glucose meals. The concentrations reaching the absorbing surfaces of the intestine being relatively the same, the rate of absorption for the various concentrations being constant, therefore, a similar stream of glucose reaches the blood independent of the concentration of the ingested meal. The blood sugar reducing mechanisms being what they are for the individual, we should then expect to find a blood sugar peak which did not change much after varying doses of glucose were given, provided the dose was adequate to provoke a peak response. However, the spread of the curve being dependent upon the continuation of a supply of glucose for absorption, the spread should be greatest after greater concentrations of glucose.

### SUMMARY AND CONCLUSIONS

Glucose meals of 5.4%, 13.5% and 25% concentrations were instilled into the stomach through a single lumen tube. With our four-lumen tube at different levels in the small intestine, the behavior of such meals was studied in their course through the intestine. From our data we have reached the following conclusions.

1. Glucose meals of high concentrations are undesirable, even when given by mouth in an individual with an intact gastro-intestinal tract, because of its irritant action on the duodenal mucosa. Such meals are particularly undesirable in individuals after gastro-intestinal anastomoses.
2. The rate of gastric emptying decreases as the concentration of the meal above isotonicity increases. Because of this, gastric emptying is an important factor in glucose absorption.
3. This decrease in the rate of gastric emptying is dependent upon the effect of the hypertonic glucose solutions as they reach the duodenum.
4. While the human stomach adds diluting fluids to ingested meals that are hypertonic, it is not the important diluting organ.
5. The duodenum possesses a remarkable versatility in shifting from an absorptive organ for glucose when solutions of low concentration reach it from the stomach to a dilution organ for solutions of high concentration.
6. When hypertonic glucose meals are of concentrations not injurious to the duodenum, the dilution mechanism of the duodenum assures a stream of glucose to the upper jejunum that is at, or below, isotonicity. Under such conditions, the small intestine, beyond the duodenum, always acts only in an absorptive capacity. The distal portions of the small intestine, however, would be able also to dilute should hypertonic solutions reach them.
7. The greatest portion of the glucose absorbed from isotonic meals is absorbed by the duodenum and upper jejunum, but as the concentration becomes higher, the absorption in these areas is proportionately smaller.
8. After hypertonic glucose meals the percentage of total glucose absorbed beyond the duodenum is unrelated to the concentration of the meal or to the

total amount of glucose absorbed. This is understandable on the basis of Paragraph 6.

9. The explanation of Cori's conclusion that the rate of absorption of glucose is independent of both the absolute amount and the concentration of sugar present in the intestine, we believe, lies in the retardation of gastric emptying and in the dilution mechanism of the duodenum resulting from hypertonic meals.

10. Osmotic pressure of fasting intestinal contents was below isotonicity at all the levels studied. After glucose the osmotic pressure in the duodenum de-

pended upon the concentration of the meal placed in the stomach. Below the duodenum, isotonicity was maintained except in the lower ileum where hypotonic conditions were found at practically all times. This leads us to believe that water absorption was greatest from the lower small intestine.

11. The blood sugar curves which resulted from the absorption of the glucose at various levels of the small intestine are discussed.

We acknowledge the technical assistance of Herman Siple, B.S. and Arthur Murray, III, M.A.

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## Factors Influencing Digestion in the Jejunum\*

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IN 1934, Miller and Abbott showed that a double-lumened tube, carrying a bag at its tip, may be used successfully to intubate the small intestine at levels lower than had been reached commonly by the tubes used for duodenal drainage (1-2). Later a triple-lumened tube with various modifications in the character of the balloon and tip was described (3). The results of numerous investigations on the chemical characteristics of intestinal juice so obtained have been reported by Miller, Abbott and co-workers (4-9). The tube, furthermore, has been used in the diagnosis and treatment of partial or complete intestinal obstruction by Abbott and Johnston (10), Wise (11), Abbott (12, 13), Wilson (14), Johnston (15), Lofstrom and Noer (16), and others. The demonstration of the practicability of this method for intubation of the lower reaches of the digestive tract is one of the most significant contributions made in the past decade to the study of gastro-enterology. Hitherto, much of the motor and secretory activity of the small intestine in man has been assumed from analogy to be similar to the behavior of the intestine of the dog, rabbit, cat and other laboratory mammals. The Miller-Abbott tube affords a logical approach to the intestine,

one with which many of the physiologic assumptions may be checked and extended in man.

Owles (17, 18, 19) has made a careful study of the enzyme content and secretory activity of isolated portions of the small intestine by the use of a tube with two bags, which when inflated, closed off a 10-15 centimeter segment. One lumen of the tube supplied the bags, another drained the segment between the bags and the third lumen opened above the upper bag. In such an isolated segment he demonstrated the presence of invertase, erepsin, lactase and lipase in significant amounts and traces of diastase. It seemed of interest to study enzyme concentrations in subjects having a mixture of all the juices of the upper intestinal tract rather than the unmixed juice of an isolated segment at a given level. Having this objective, the present report is concerned with the digestive activity of mixed secretions reaching the jejunum in a variety of subjects.

## METHOD OF STUDY

In place of using an isolated segment, all digestive secretions from the mouth, stomach, liver, pancreas and intestine were allowed to accumulate above a single bag inflated in the jejunum. One opening of the triple-lumened tube extended below the bag (enabling one to check against leakage of fluid past the bag), another lumen opened immediately above the

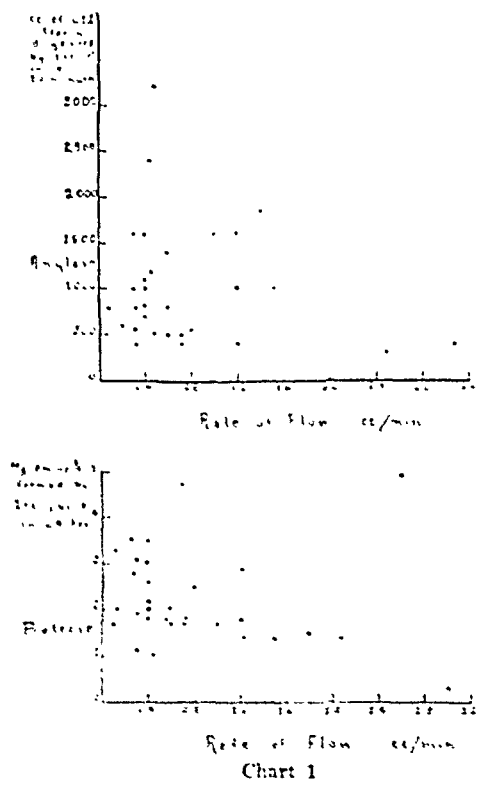
\*From the Medical Clinic of the Peter Bent Brigham Hospital and the Departments of Medicine and Biological Chemistry, Harvard Medical School.

bag. After the tube was passed into the stomach, the subject was placed behind a fluoroscope and the Morgenstern (20) maneuver used to facilitate the passage of the lead bucket and bag through the first portion of the duodenum and into the descending segment, if possible, before inflating. If the bag was inflated in the first segment of the duodenum it occasionally remained there, delaying passage into the jejunum for an hour or so. The position of the tube was estimated both by the length swallowed and by the position of the metal tip in the fluoroscope. Because of the sleeve-like accumulation of intestine above the inflated bag on an otherwise stationary tube, one cannot be sure of the exact level of collection of juice, but for the most part the observations were on specimens drawn from the upper or mid-jejunum (90-120 cm. from the teeth of the subject). When it was desirable to have the tube progress down the intestine, it was found better to maintain air at a constant volume in the bag rather than a constant pressure.

Estimations of two enzyme activities were made by the same methods as employed by Owles (18) as follows:

**Protease:** Two test tubes, 200 by 20 mm., were set up, each containing 10 cc. of 0.5% gelatin, 5 cc. of phosphate buffer (pH 6.8) and 0.5 cc. toluene. To one tube was added 1 cc. unboiled intestinal juice; to the other 1 cc. of boiled intestinal juice as a control. The tubes were shaken and incubated for 24 hours at 38

Comparison of Rate of Flow of Jejunal Juice with Enzyme Activity



Proteolytic activity of jejunal juice fasting and after various stimuli. (Expressed in milligrams of amino nitrogen liberated by 1 cc. of juice from a 2.5% gelatin solution after 24 hours incubation at 38° C)

N	Fasting	After MCI	After Maltose	After 0.2% Starch	After 0.2% Gelatin	After 0.2% Casein	After 0.2% Pepsin
1	1.0	1.0	1.0	1.0	1.0	1.0	1.0
2	1.0	1.0	1.0	1.0	1.0	1.0	1.0
3	1.0	1.0	1.0	1.0	1.0	1.0	1.0
4	1.0	1.0	1.0	1.0	1.0	1.0	1.0
5	1.0	1.0	1.0	1.0	1.0	1.0	1.0
6	1.0	1.0	1.0	1.0	1.0	1.0	1.0
7	1.0	1.0	1.0	1.0	1.0	1.0	1.0
8	1.0	1.0	1.0	1.0	1.0	1.0	1.0
9	1.0	1.0	1.0	1.0	1.0	1.0	1.0
10	1.0	1.0	1.0	1.0	1.0	1.0	1.0

Observations  $\pm$  5 minutes after instilling solution indicated  
Chart 2

degrees C. At the end of the digestion the contents of each tube were added to 7 cc. neutralized, 40% formaldehyde for the Sørensen (formol) titration. The results (after subtracting the blank) were expressed as milligrams of amino nitrogen formed by 1 cc. of juice after 24 hours' incubation.

**Amylase:** Ten tubes containing graded amounts from 0.05 cc. to 0.50 cc. of jejunal juice were set up with 0.5 cc. of M/10 phosphate buffer (pH 6.8) and 1.0 cc. of 0.2% starch solution and made up to 3 cc. with water. Additional tubes containing 0.6, 0.7, 0.8, 0.9, 1.0 and 1.5 cc. of juice, respectively, were set up in the first estimation of each specimen to determine the range of activity and necessary dilution of the juice for subsequent checks. After incubation at 38

Amylolytic activity of jejunal juice fasting and after various stimuli. (Expressed in units = the number of cubic centimeters of 0.1% soluble starch digested by 1 cc. of juice in 30 minutes at 38° C)

Units	Fasting	After MCI	After Maltose	After 0.2% Starch	After 0.2% Gelatin	After 0.2% Casein	After 0.2% Pepsin
3500	1.0	1.0	1.0	1.0	1.0	1.0	1.0
3000	1.0	1.0	1.0	1.0	1.0	1.0	1.0
2500	1.0	1.0	1.0	1.0	1.0	1.0	1.0
2000	1.0	1.0	1.0	1.0	1.0	1.0	1.0
1500	1.0	1.0	1.0	1.0	1.0	1.0	1.0
1000	1.0	1.0	1.0	1.0	1.0	1.0	1.0
500	1.0	1.0	1.0	1.0	1.0	1.0	1.0
0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
0	1.0	1.0	1.0	1.0	1.0	1.0	1.0

Observations  $\pm$  5 minutes after instilling solution indicated  
Chart 3

degrees C. for exactly 30 minutes, the achromic point with iodine in the series of digestion tubes was recorded. The results were expressed as cubic centimeters of 0.1% starch solution digested by 1.0 cc. of juice.

### COLLECTION OF DATA

Forty-nine observations were made on thirty individuals. Eleven of this group were normal men or

TABLE A

	No. Subjects	No. Observations
Normal individuals	11	15
Achlorhydria	5	12
Resection	5	8
Peptic ulcer	4	8
Cholecystectomy	3	3
Gastro-enterostomy	1	2
Sprue	1	1
Total	30	49

women. Nineteen were patients with achlorhydria, peptic ulcer, or those having had a cholecystectomy, gastric resection or gastro-enterostomy as indicated in Table A. The fasting rate of flow of the juice was irregular, varying both from sample to sample and from patient to patient. Observations on 31 samples indicated rates varying from 0.08 cc. to 4.0 cc. per

achlorhydria, peptic ulcer or following cholecystectomy, as compared to the group of apparently normal adults.

A study was made of the effect of various chemical and food solutions on intestinal enzymes. The observations recorded in Charts 2 and 3 are from samples taken forty-five minutes after various stimuli; the elapsed time was allowed so that the transport of water and electrolytes through the bowel wall might correct for the dilution effect. These stimuli were solutions of N/10 HCl, 5% MgSO<sub>4</sub>, 10% iron and ammonium citrate, 2% gelatin, 1% starch and a 5% amino acid mixture,\* each in 100 cc. volumes which were placed through the tube directly into the jejunum above the inflated bag. The samples had approximately the same scatter of proteolytic and amylolytic activity as was present in fasting juice.

In order to determine the dilution and the influence of abrupt chemical changes on enzyme activity, we now carried out serial observations in individual subjects. One hundred cubic centimeters of water were introduced directly into the jejunum above the inflated bag. The latter was kept well-distended to prevent escape of the fluid to the lower tract. As seen in Chart 4, the effect on both proteolytic and amylolytic activity was virtually the same. A definite decrease occurs in 5-10 minutes from which there is a return to normal in 15-20 minutes.

The effect was determined of an isotonic solution of sodium bicarbonate and of a tenth-normal solution of hydrochloric acid in 100 cc. amounts. (Charts 5 and

### Distilled H<sub>2</sub>O into Jejunum

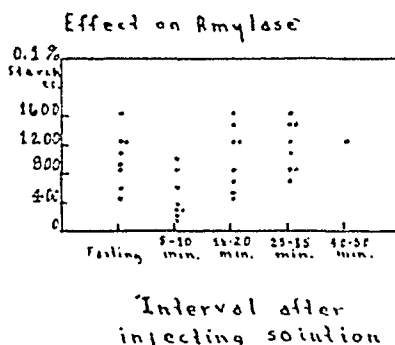
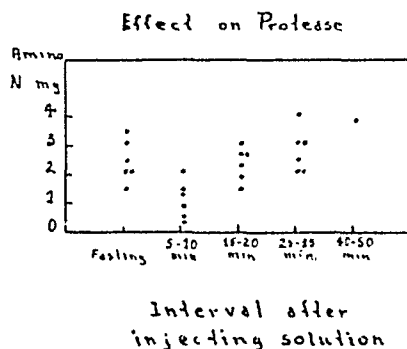


Chart 4

minute, with a mean flow of 0.8 cc. per minute for the entire group.

Enzyme activity of jejunal juice obtained in the manner described, with no stimulus other than the presence of the tube and bag, is designated in the graphs as "fasting." A wide variation in protein-splitting ability was noted: 1 to 5 mg. of amino nitrogen may be formed by 1 cc. of juice. (Chart 1) The fasting starch-splitting activity ranged from 1060 cc. to 3600 cc. (an average of 44 observations was 1060 cc.) of 0.1% solution of soluble starch digested by 1 cc. of jejunal juice in 30 minutes at 38 degrees C. These variations in enzyme titer bore no relation to the rate of flow. No significant difference in the enzyme titers of the first or subsequent specimens of juice was found in patients with gastric resection,

6) Chart 5 shows that an isotonic solution of sodium bicarbonate essentially produced a diluting effect on protease with a return to normal in 15-20 minutes. It is interesting that the amylase appeared slightly more depressed and its normal activity did not return until after 40 or 50 minutes. Following hydrochloric acid instillation the proteolytic activity in the jejunum returned to the original level after 30 to 40 minutes. (Chart 6) Starch-splitting ability of jejunal juice is seriously interfered with by the dilute acid, more by its destructive action on amylase than by simple dilution. However, 40 to 50 minutes after using hydrochloric acid, good amylase activity is again present. The effect of introducing a 5% solution of amino acids

\*Product 92Z furnished by Mend Johnson and Company.

was not significant. This solution exerted a diluting effect with but slight delay in return of proteolytic and amylolytic activities. (Chart 7)

A summary of the effects of these solutions on enzyme content is given in Chart 8.

One-tenth normal hydrochloric acid when placed directly into the jejunum caused a mild burning sensation referred by the patient to the upper abdomen, a marked increase in motor activity of the intestine on the balloon (noted on a water manometer), nausea and a momentary flushing of the skin of the face and neck in one-third of the patients. Others had no awareness of the instillation of dilute acid. All so-

to be removed from this level of the jejunum (after correction for the volume administered) was usually 300 to 500 cc. in the course of one hour. Thus, the secretin effect of the acid in the bowel so increases the rate of flow that the total amount of enzymes available subsequently may be 10 to 20 times that in the fasting juice under the condition of the experiment.

### DISCUSSION

Our observations on the irregularity of flow of the fasting specimens confirm the previous report of Karr and Abbott (4) who found rates of flow of 2 cc. or less

### Isotonic $\text{NaHCO}_3$ into Jejunum

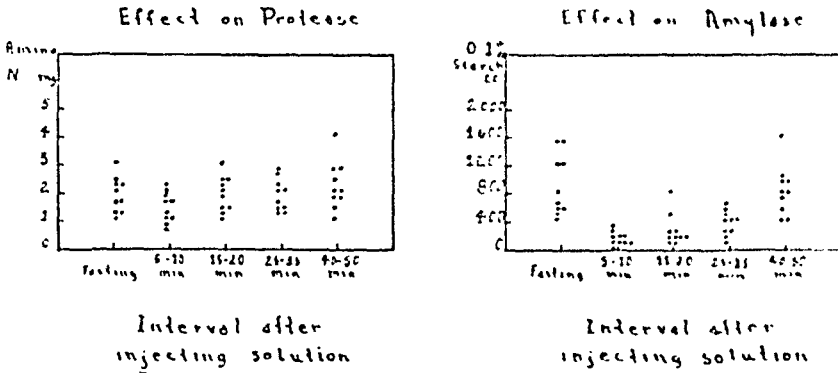


Chart 5

### N/10 HCl int. Jejunum

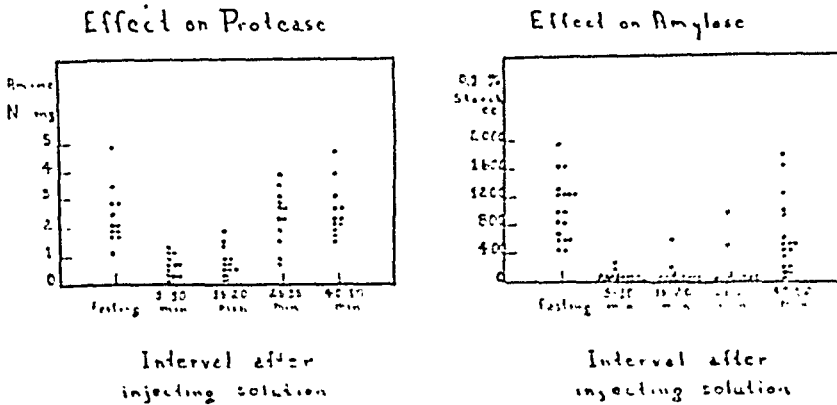


Chart 6

lutions were warmed to body temperature before administration. No patient received any sensation below the level of the throat from the use of 100 cc. amounts of water, 1.3% sodium bicarbonate, or the mixture of amino acids.

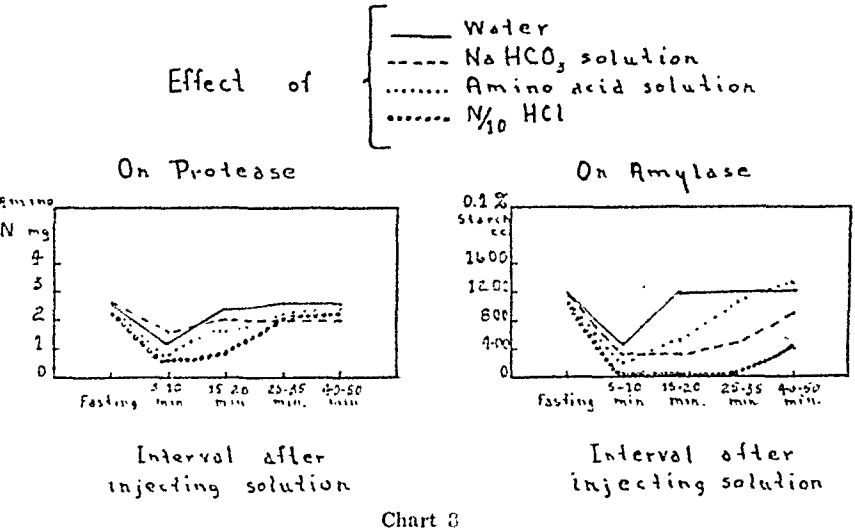
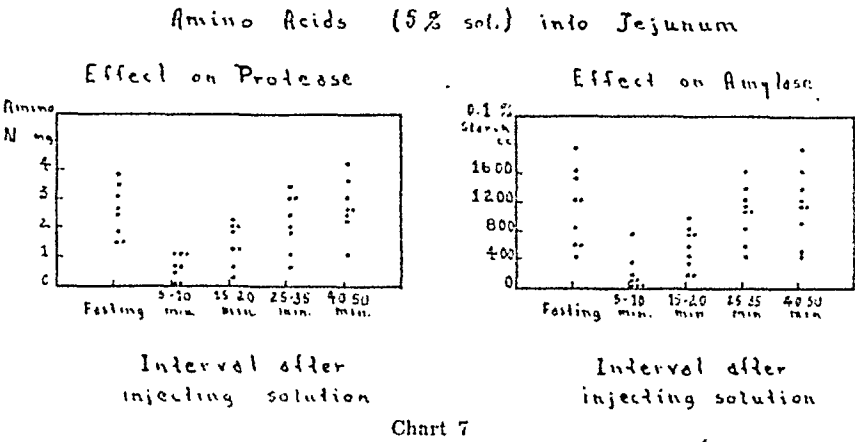
It was observed that while no increase in relative enzyme concentration could be demonstrated, hypertonic solutions, or any concentration of hydrochloric acid used was followed by an increased rate of flow of jejunal juice (increase in total volume with the enzyme concentration approximately the same). Following 100 cc. N 10 HCl the total volume of juice

per minute in 45 out of 65 fasting specimens from the small intestine and noted a marked tendency to intermittency even though an admixture of substances from above the site of collection was permitted. Miller and Karr (6) later reported the rate of flow from normal subjects to be 30 cc. or less per hour for 17 samples and between 30 and 100 cc. per hour for 13 samples. During intubation, distension of the bag stimulates fairly regularly the flow of intestinal fluid in human subjects. During any resting period with a constant flow for a short interval, it was found that additional distension of the bag resulted in increased

rate of flow of the segment involved. This was noted by Miller, Abbott and Karr (7) and Owles (17). These observations confirm the belief of surgeons that intestinal obstruction due to strangulation is associated with an increased flow of digestive juices. However, they are not in harmony with the studies of Montgomery (21) on Thiry-Vella dogs in which he could not demonstrate hypersecretion of duodeno-jejunal loops with balloon distension. The reason for this difference between Thiry-Vella loops and the normal human intestine is not apparent. We observed a marked variability in motility of the jejunum, not

(18). Animal experimentation suggests a tendency toward an increased enzyme content when rates of flow are slower (22). We were unable to determine such a correlation between the rate of flow and enzyme titer.

The most striking feature in our experiments is the rapidity with which the intestinal contents become readjusted. The greatest disturbance which we found was the depression of amylase activity after the introduction of hydrochloric acid. But even in this situation, there was a return to normal within 40-45 minutes. In contrast to this, Owles (18, 19), was not



only from individual to individual, but in the same individual from day to day. Many factors affecting the autonomic nervous system must influence the intestinal motility, although Miller and Karr (6) observed a more or less fixed rate of motility for the individual subject during intubation on separate days. Perhaps this difference may be accounted for by a difference in the subjects used. Wide variations of enzyme activity have been previously reported for both humans and dogs. This has been emphasized by Cajori (22) for Thiry-Vella loops in dogs and by the work of others which has been carefully reviewed by Owles

able to demonstrate any such re-establishment in isolated loops.

Furthermore, Owles noted a tendency to exhaustion of the enzymes in an isolated loop following prolonged stimulation (19). This was not noticed in our cases where the jejunum was not separated from the duodenum.

It is probable that these differences may depend upon the fact that we did not use a closed loop; thereby, permitting a greater mixing of secretions and more nearly approaching the normal conditions of the intestinal tract. It would seem probable that the

readjustments are facilitated by a free communication throughout the tract. If equilibrium is disturbed in a small area a rapid mixing of juices will aid in overcoming this disturbance. Furthermore, if the pancreas responded to the introduction of hydrochloric acid through the latter's secretin effect, it is possible that fresh pancreatic amylase entered the jejunum after hydrochloric acid was neutralized in our experiments. Such a mechanism could not influence the contents of an isolated loop below the pancreas.

Rosenthal (23) has suggested that an inhibition of adequate pancreatic digestion by the increased amount of acid coming from gastric hypersecretion may explain some of the digestive and metabolic disturbances in such individuals. The results of our studies suggest that the duration of such an inhibition is probably too short to be of much importance. We have found that a shift in the electrolytes corrects for the presence of hydrochloric acid in the jejunum with remarkable efficiency in both normal and diseased subjects. This ability of the intestinal tract to make readjustments can explain the absence of clinical evidence of significant interference with digestion after the use of large doses of alkalis, the paucity of disturbances in patients with achlorhydria or those with abnormally high acid values. These findings suggest that the disturbances occasionally noted in hyperchlorhydria and achlor-

hydria are more likely to have a basis in the motor behavior of the bowel rather than in significant or persistent changes of enzyme activity secondary to acid-base variations.

### CONCLUSIONS

1. The amylase and protease content of the jejunum in normal subjects and in patients with peptic ulcer, achlorhydria and those having had resection or cholecystectomy have been investigated by intestinal intubation.
2. Solutions of magnesium sulphate, iron and ammonium citrate, gelatin, starch, amino acids, sodium bicarbonate and hydrochloric acid had no demonstrable effect on the starch and protein-splitting ability of the jejunal juice after an interval of 45 minutes.
3. Serial observations showed an immediate decrease of enzyme activity followed by a rapid return to a normal concentration of enzyme activity in the jejunum after the instillation of N/10 hydrochloric acid, 5% solution of amino acids, isotonic solution of sodium bicarbonate or distilled water.
4. No significant variations in the enzyme content of the jejunal juice was observed between the different types of subjects investigated.

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# Intubation Studies of the Human Small Intestine

## XX. The Diagnostic Significance of Motor Disturbances\*

By

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ANY lesion of the small intestine, irrespective of its nature, is much like a mill dam in a stream. The current is held back above the involved area and accelerated immediately below it. These two processes, in respect to an intestinal lesion, are reflected in the symptomatology of the disorder, and under varying circumstances either may predominate. In its milder form, this obstructive syndrome may equally well re-

formation visualized at the site of the suspected lesion. This work was carried further in our clinic by Boon (4). In addition Abbott and Johnston (2) pointed out that a record of small intestinal muscular activity is of diagnostic value. On the basis of kymographic records from the balloon on the end of the intestinal tube, Abbott, Zetzel and Glenn (5) were able to describe the characteristics of intestinal contractions in the presence of a high degree of obstruction. The present presentation covers an extension of their study to the field of small intestinal disturbances in general, in an effort to analyze the motor activity of the bowel in all types of patients who exhibit some phase of the obstructive syndrome. From this study, we believe that we have arrived at a clearer understanding of the pathogenesis of certain small intestinal symptoms.

### METHOD

Balloon systems have long been used in recording intestinal activity in animals, but it was Ganter (6) in 1921, who first applied the method to the normal intact human subject. An improved technique was used by Abbott and Pendergrass (7) and by Elsom, Glenn and Drossner (8) in their studies of drug effects. The latter procedure is also well suited to clinical use. Air displaced from the balloon of a Miller-Abbott intestinal apparatus is graphi-

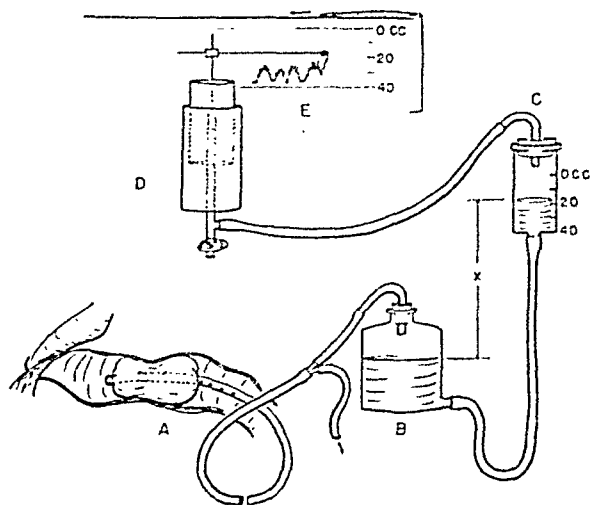
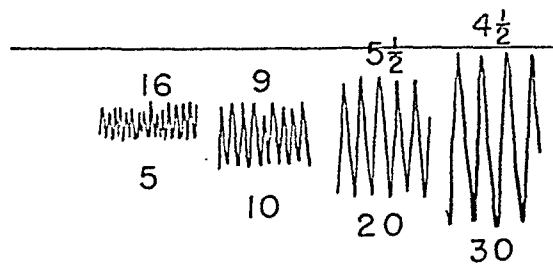


Fig. 1. The recording apparatus. A. A tube and balloon in the intestine. B. Lower fluid reservoir. C. Upper calibrated fluid reservoir. D. Spirometer-type volume recorder. E. Calibration of the paper corresponding to that of the upper reservoir. X. The hydrostatic pressure exerted on the air in the balloon.

sult from a persistent spasm, such as that reported near calcified mesenteric lymph nodes (Golden (1)) or from organic narrowing, such as may be produced by a band of adhesions. The nature and modus operandi of these two forms of obstruction cannot, however, be properly appreciated by ordinary diagnostic procedures. As an aid in the solution of this problem, Abbott and Johnston (2) described the use of the Miller-Abbott (3) method of small intestinal intubation as a supplement to roentgenological investigation, since by that combined procedure an opaque medium can be injected directly and its exact con-

### SENSITIVITY CALIBRATION WAVES PER MINUTE



### C.C. DISPLACED/WAVE

Fig. 2. The recording speed of the system.

cally recorded by a spirometer type volume recorder (Fig. 1, A and D). The recorder and the condom balloon are each capable of holding 40 cc. of air. To prevent peristalsis from emptying the balloon too readily, a hydrostatic unit (Fig. 1, B and C) is inserted into the system. This not only exerts a pressure equal to the difference in height of the fluid levels in the two bottles (Fig. 1, X), but also provides a damping effect which minimizes arti-

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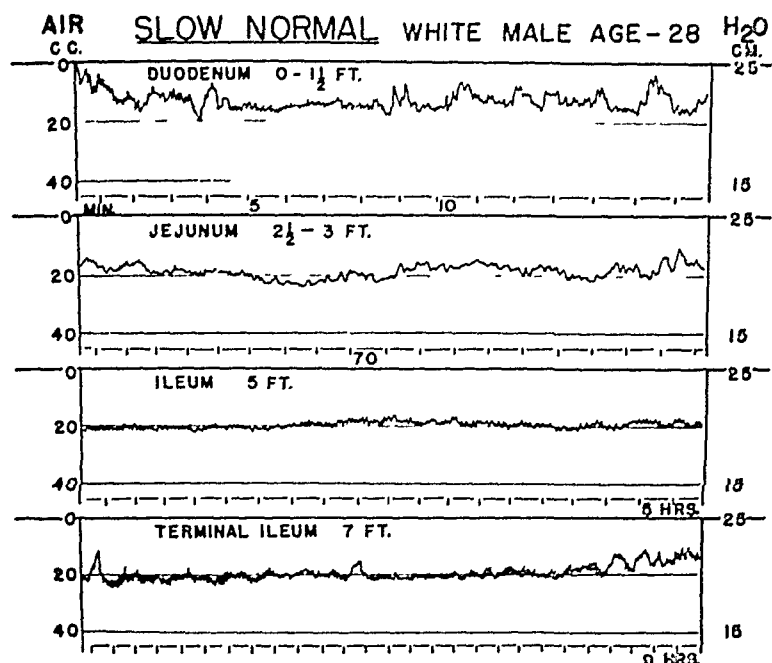


Fig. 3. *Low normal activity.* The record was made from a phlegmatic young paid subject who has never had digestive symptoms.

facts due to breathing and to body movement. The sensitivity of the instrument, however, is adequate for recording intestinal movements (Fig. 2). If the upper vessel is calibrated, the volume of the balloon at any moment can be noted.

#### SUBJECTS

A total of 76 records was obtained on 64 subjects. While some of the records represent practically continuous tracings as the balloon passed from the duodenum to the colon, many were made from selected areas of the gut. Four of the subjects were normal individuals from whom ten tracings were made. Seventeen of the others were operated upon, while 22 of the remaining 43 were followed clinically for a period of at least 6 months. Routine roentgenological studies of the gastro-intestinal tract

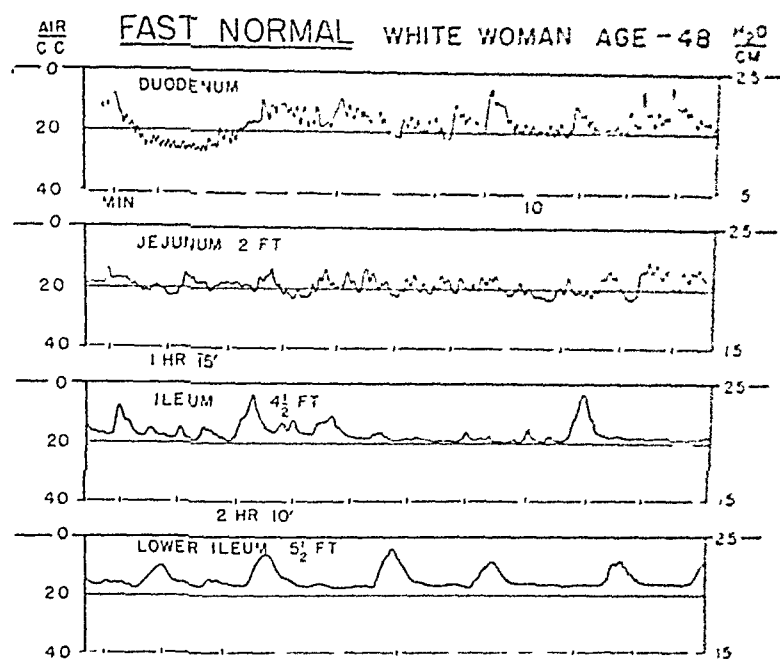


Fig. 4. *High normal activity.* This woman, a normal paid subject, invariably becomes nauseated and uncomfortable as the day advances.

were made on all the patients. Other laboratory procedures were carried out as indicated.

#### PROCEDURE

When the tip of the tube has traversed the descending duodenum, the record is started and the balloon is inflated under a 25 cm. water pressure created in the hydrostatic unit. Once under way, the tracing may be continued until the balloon has reached the colon, but this is rarely necessary. After the balloon has passed 2 feet beyond the duodenum, an adequate impression of muscular activity is obtained if the passage of every alternate foot of tubing is recorded. A continuous record is indicated, however, if the patient experiences pain or the balloon is arrested. When recording is omitted, the patient should move about

#### SMALL WAVES - X-RAY AND TRACING

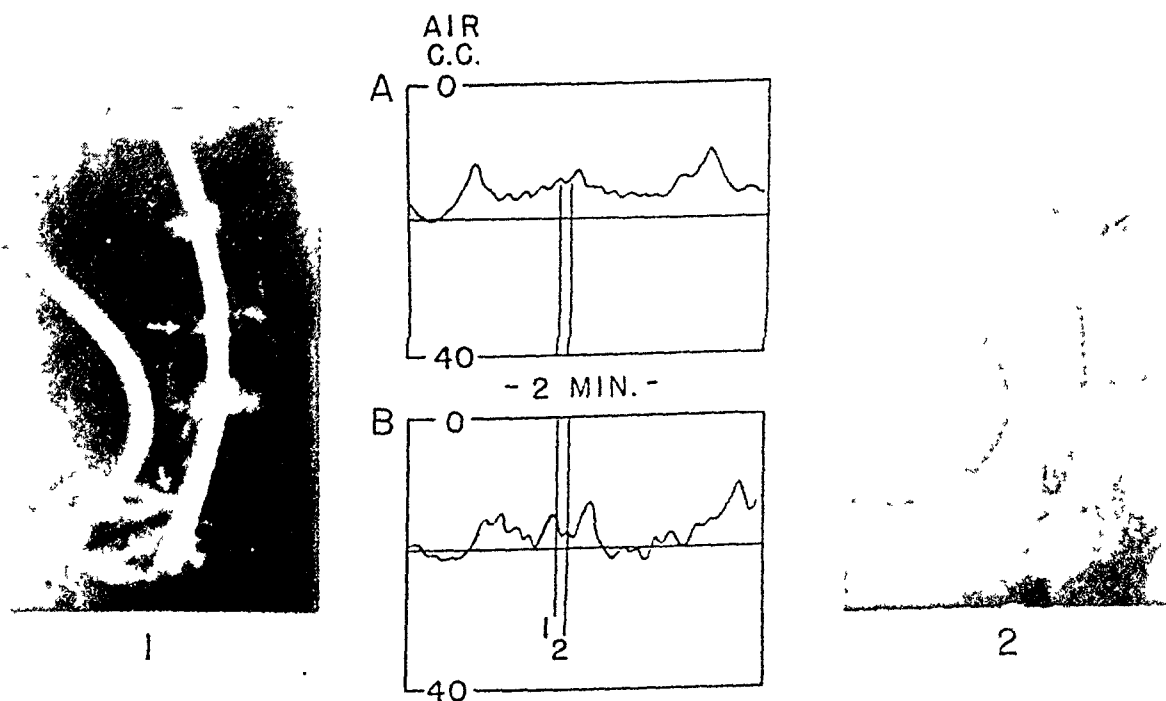


Fig. 5. *A correlation of intestinal activity with S waves on the record.* Films 1 and 2 were exposed at the corresponding points on the record. Fluoroscopy before and after the films showed that the S. waves indented the balloons (arrows) and progressed caudad. Most waves could be traced from the proximal end of the proximal balloon A to the distal end of the lower balloon B, but sometimes the waves appeared in the middle of the balloon or died out before reaching the distal end. None was seen to remain stationary.

and preferably eat something, but during the test he must lie quietly. Suction should be applied to the gut lumen above the balloon if he eats. When a balloon has not advanced in 3 hours, a local lesion should be suspected. Under such circumstances, the kymographic phase of the diagnostic intubation ends, and at that time the roentgenological phase of the procedure should begin with the injection of an opaque medium down the tube. Ordinarily by starting in the morning, the study is completed by late afternoon, though in cases of depressed motility it has been necessary to re-examine the patient the next morning to determine whether or not the balloon has entered the cecum.

### RESULTS

The nature of the record obtained by this method is shown in Figs. 3 and 4, in which the normal range of

minute, at times compressed the balloons throughout their entire length. Ordinarily both types continued simultaneously, though either might appear independently (Fig. 12).

So many descriptive terms have been used for intestinal movements and so many species differences among laboratory animals have been described that the terminology is confused. Although the small waves may be those described by Alvarez (9) as rhythmic myogenic contractions of an advancing type, and although the large ones may be due to peristalsis in the Bayliss and Starling (10) sense, we shall simply define these waves which are characteristic of the balloon technique as L (large) and S (small) waves.

Figs. 3 and 4 show the typical tonus levels. From

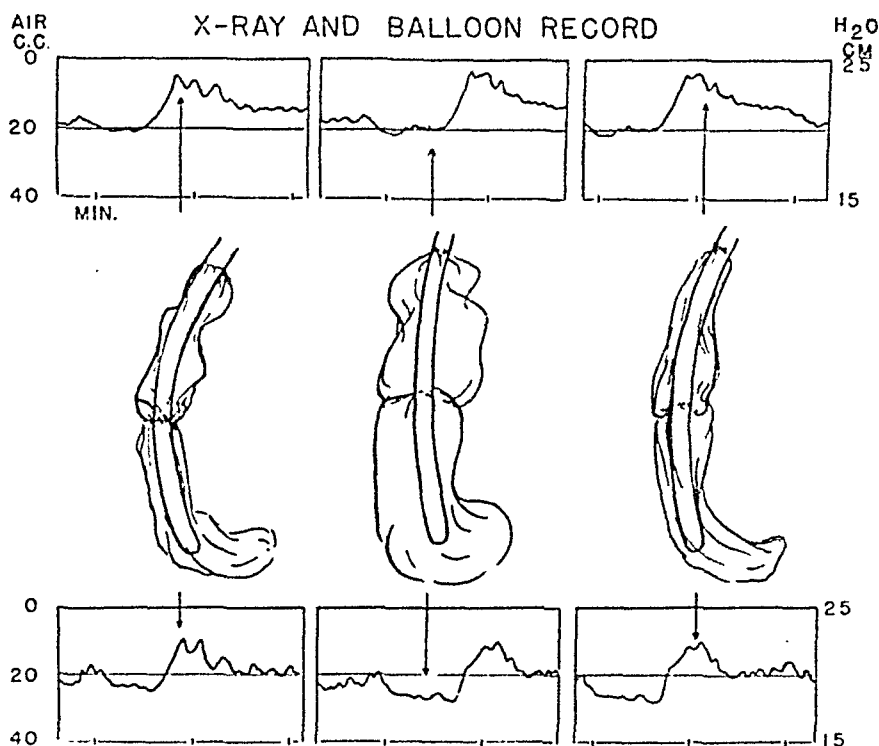


Fig. 6. A correlation of intestinal activity with L waves on the record. The three drawings of the balloons were traced from films exposed at the points indicated. While the L waves were slowly compressing and releasing the entire length of both balloons in a wave that always involved the proximal balloon first, the small S waves could be seen superimposing narrow contractions on the surface of the generally compressed balloons.

sample tracings from the duodenum, jejunum, ileum and lower ileum of symptom-free subjects is presented. The familiar pattern of a general tonus level and of two types of wave, one small and rapid, the other large and slow, can be seen as on any balloon record from animal or man. To correlate the waves with the intestinal activity producing them, the behavior of two tandem balloons with radio-opaque walls was recorded while the subject was being fluoroscoped. Both types of wave were visualized as contractions which for the most part traveled caudad over both balloons in sequence. The small waves, coming at a rate of 5 to 9 per minute, produced narrow indentations; the large ones, often occupying one entire

the duodenum to the ileum a fall in tonus occurred and was followed by a rise as the terminal ileum was reached. Fifty-four unselected records reveal that, under the conditions of our technique, the duodenum permits an average balloon volume of 20 cc., the jejunum of 24.5 cc. and the ileum of 27 cc. In 18 of the cases in which the terminal ileum was reached, the average balloon content was 19 cc.

The S waves, the L waves and the tonus level combine to form the pattern of the record. In the duodenum, large arrhythmic L waves were common and the amplitude of the S waves was larger than in other regions. Neither periods of atony, nor spasm lasting more than one minute nor large fluctuations of tone

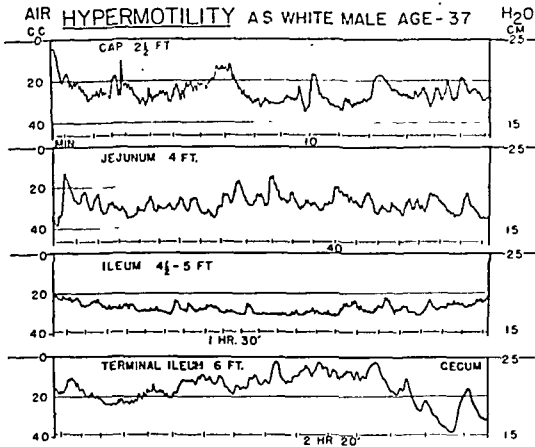


Fig. 7. Intestinal pattern associated with very rapid motility.

involving more than one-half of the balloon volume appeared in the symptom-free subject. In the jejunum, S waves were still prominent, but the L waves decreased in number as well as in size. In the ileum, the pattern was characterized by small S waves traveling along a straight or slowly undulating line. In the terminal ileum, the pattern approached that of the duodenum, but the excursions in balloon volume were usually less.

The resultant effect of the peristaltic waves and of the tone determined the rate at which the tube moved down the intestine. With few exceptions duodenal passage was effected in less than 5 minutes. In the average patient the jejunum was traversed in 2 hours, while from 3 to 6 hours were necessary to pass

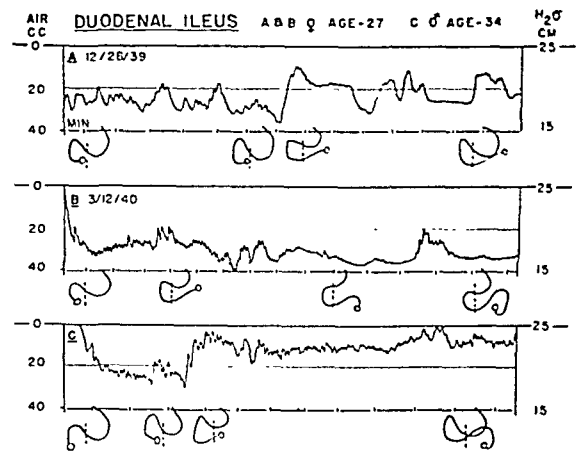


Fig. 8. Records of chronic duodenal ileus. The pattern associated with a tendency for contents to pool in the right side of the duodenum in the absence of an anatomical obstruction is shown in two patients. In one the disappearance of the hypertonic state to the left of the mid-line is shown in the tracing taken 3 months later.

through the ileum. Of the 29 records in which a duodenum-to-cecum time could be measured, 18 took between 4 and 9 hours.

The presence of gastro-intestinal symptoms was associated with deviations from the normal pattern. Even the nausea and distress which some sensitive persons experience during intubation were often accompanied by L waves of a type seen in the ileum record of Fig. 4. Though not the case in this particular instance, such symptoms were usually associated with a slow motility. Rapid motility, with duodenum-



Fig. 9. Roentgenologic appearance of chronic duodenal ileus. Film of the duodenum from which (Fig. 8-A) was made.

cecum times of less than 4 hours, has been seen only in patients with pronounced symptoms. The fastest was 2 hours and 20 minutes, recorded from a man with asthma, food allergy, a healed duodenal ulcer and unidentified calcifications in the abdomen. His tracing (Fig. 7) shows large S waves and frequent L waves on a low tonus level. A marked rise in tonus occurred in the terminal ileum. Rapid passage has twice been noted in patients suffering from renal calculi.

Exemplifying another disorder, probably of functional origin, are the records in Fig. 8 obtained from two cases of chronic duodenal ileus, which in both instances was part of a more widespread disorder. R. F., a woman of 27, had been an invalid for 15 years, had twice been operated upon under the diagnoses of tuberculous peritonitis and intestinal adhesions, but was admitted to our hospital unimproved and in an advanced state of cachexia. Anorexia, nausea and

with dense peritoneal adhesions in the left lower quadrant of the abdomen, the result of a former traumatic perforation of the bowel. Though able to adjust himself fairly well, he suffered intermittently from colicky pain and distension (Fig. 10). Following his death a year later from unrelated causes, an autopsy confirmed the diagnosis. A balloon tracing (Fig. 11) showed exaggerated jejunal activity followed by a progressive fall in tone as the balloon approached the narrowed area. As the diameter of the gut enlarged, the amplitude of the L waves increased and the S waves disappeared, while just above the obstructed area, all evidence of muscular activity was absent.

Arrest of the balloon from spasm also occurs. E. R., a middle-aged woman with gall stones, exhibited such a condition (Fig. 12-A), the L waves suggesting an obstruction but the gut lumen maintaining its usual

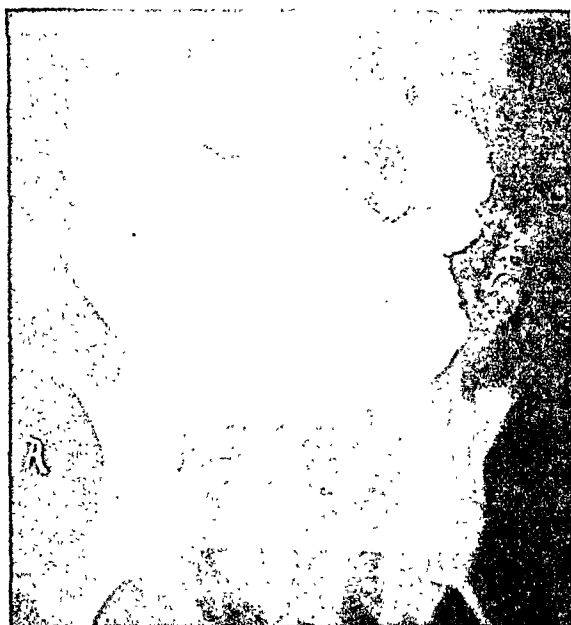


Fig. 10. Roentgenograms of a partially obstructed intestine. The appearance on two different occasions after the giving of barium sulphate meals by mouth.

vomiting were marked when the record shown in Fig. 8-A was obtained. A roentgenogram (Fig. 9) confirmed the impression of duodenal ileus. After 3 months of systematic encouragement, exercise and a high vitamin diet, a gradual abatement of her symptoms and a return of appetite occurred with a change in duodenal function as indicated in Fig. 8-B. The second patient (Fig. 8-C), a man of 34, was admitted with the same symptoms after 8 years of semi-invalidism and two ineffective abdominal operations. In the case of R. F. in particular, the abnormalities were by no means confined to the duodenum, wide fluctuations of tonus and wave effect being apparent throughout.

Most important, however, because of their possible prognostic significance were the records showing delay or arrest of progress. Actual organic partial obstruction was present in N. G., a man of 67, admitted

caliber. At operation no organic lesion of the intestine was found. The record of D. S., a woman whose appendix had been removed for chronic right lower quadrant pain without subsequent improvement, suggested obstruction (Fig. 12-B) when the balloon was temporarily arrested in the terminal ileum. Here too the tonus remained normal, and the S waves remained prominent on the tracing. A barium suspension injected into the gut lumen was observed to flow promptly into the cecum without regurgitation (Fig. 13). Finally V. E., partially obstructed at the recto-sigmoid by dense adhesions, showed a normal ileal record (Fig. 12-C) which changed to an abnormal pattern when a milk and molasses enema began to elicit low abdominal pain. Similar ileal tracings showing smooth, large L waves on a rather average tonus level were observed to occur near calcified

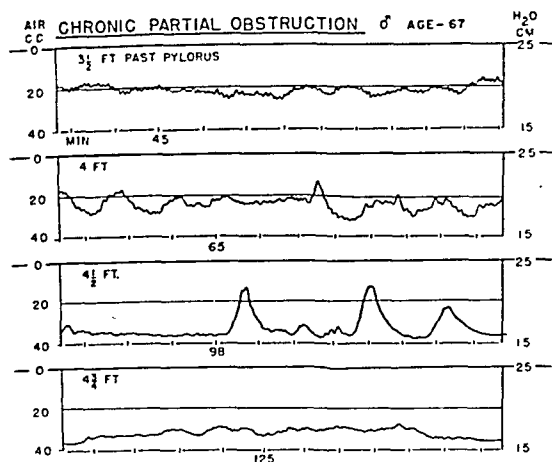


Fig. 11. A tracing of partial intestinal obstruction. The falling tonus, disappearance of S waves and the increasing amplitude of the L waves as the lesion is approached are clear cut. The fading out of activity in the "decompensated" gut immediately proximal to the partial obstruction is also seen.

mesenteric lymph nodes and in the presence of diseased or disfunctioning gynecological organs.

### DISCUSSION

Since a record of intestinal activity deals with contractions and tonus and with the resultant motility of the contents, interpretation must depend on the interrelation of these factors. This is more apparent when we recall that tonus as we use the term means intestinal caliber. Peristalsis in a tightly contracted gut cannot move the contents for lack of "diastolic" relaxation between waves or, in other words, because the waves are necessarily of low amplitude. To gain amplitude and in turn motility, a certain degree of widening between waves must occur. When, on the other hand, the optimal degree of dilatation for maximal motility of contents per wave has been exceeded, the efficiency of peristalsis is diminished, probably due to "leakage" orad past the advancing wave, as suggested by Brinton (11) in 1859. Finally, a degree of distension is reached which precludes peristalsis altogether. If the interdependence of these three factors is realized, hypermotility, as evidenced in Fig. 7, is seen to depend not only on the active wave pattern but also on the generally low tonus. The same explanation is applicable to diseases like sprue, in which diarrhea may occur in association with marked relaxation of the gut.

In the patients with generalized intestinal hypermotility and in patients such as the ones from whom tracings 8-A and 8-C were taken, in whom hypomotility occurs in association with abnormal tonal fluctuations and a deranged wave pattern throughout the small bowel, the records help to clarify the symptoms and the part played by the digestive tract in their production.

The chief clinical importance of recording the abnormalities of the small intestine lies, however, in distinguishing a local lesion from a generalized and systemic disorder. The characteristic effect of the local lesion is the obstructive pattern. In its milder form

this consists of the gradual disappearance of the S waves and the emergence of large, smooth L waves which may cause the patient pain. If the obstruction persists, the gut lumen dilates and on the record the tonus falls as the balloon approaches the lesion, while the L waves become even larger but finally disappear as muscular activity wanes. The obstructive pattern, especially its mild form, appears typically in any area where progress of the balloon is halted, even during the transient arrest which may occur at an angulation of the gut in a patient who remains too immobile during the test. Though any local disturbance, whether a normal angulation, a spasm or an organic occlusion, may produce the obstructive pattern, the duration of the arrest, the size of the L waves and the changes in tonus level are proportional to the severity of the lesion.

The data obtained from the records has the following diagnostic significance: Firstly, if the balloon enters the cecum in 9 hours or less, an organic lesion of the small intestine is, in our experience, ruled out. If the tracing is normal, it makes this negative evidence more conclusive. Secondly, an abnormal pattern throughout the gut indicates a generalized disorder. Thirdly, if in the presence of an obstructive pattern the tube is arrested for more than 3 hours in spite of the patient's eating and moving about, the cause is more likely to be organic than spastic. Further evidence in favor of a mechanical block is adduced by the appearance of the complete obstructive pattern.

The criteria by which a local lesion is identified are most clear-cut in advanced cases that may be diagnosed by less arduous means; while in the cases of a minimal lesion in which other diagnostic measures fail, the changes in the tracing are also less decisive. Nevertheless, the combined results of a diagnostic intubation (e.g. the determination of arrest in the balloon's progress, the visualization of the area in which the arrest occurs by the local injection of an opaque medium and the picture of the muscular reaction of the gut as indicated on the kymograph) offer

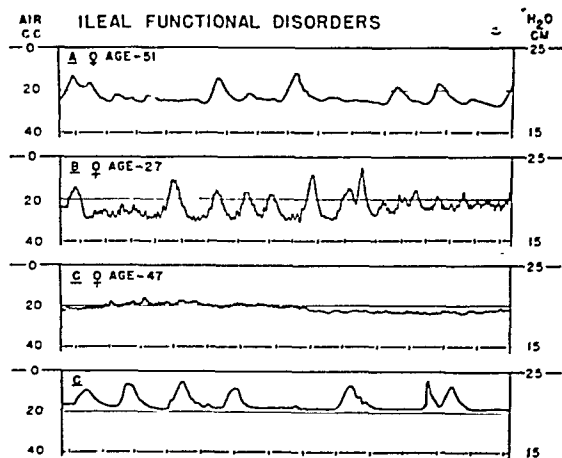


Fig. 12. Tracings from the ileum. A. An obstruction-like pattern without falling tonus, due to a functional disturbance in a woman with gall stones. B. Spasm of the terminal ileum. C. The ileum unaffected by a partial obstruction of the low colon. D. The same ileal area after irritation of the colon.

evidence which may be of great help in arriving at the proper diagnosis.

As a diagnostic test, this method is limited in its applicability to a small group of patients: (1) those who because of suspected intestinal obstruction should not ingest a barium sulphate meal; (2) those who by gastro-intestinal roentgenography are shown to have a disturbed small intestinal picture without clearly diagnostic findings and (3) those who suffer from persistent abdominal symptoms which other methods fail to clarify.

### CONCLUSIONS

On the basis of 76 kymographic records of intestinal activity obtained by intestinal intubation from 64

well-controlled subjects, including both normal individuals and patients, the following conclusions seem justified:

1. That such a diagnostic study is practical.
2. That three types of observations can be made: (a) on the caliber of the small bowel, (b) on the pattern of its large and small waves and (c) on the motility of its contents.
3. That such observations offer in many otherwise obscure cases objective data for an opinion as to the existence of a functional or organic basis for intestinal symptoms and as to the existence of a local or general small bowel involvement.



Fig. 13. Roentgenogram of the terminal ileum. A barium sulphate suspension injected down the tube immediately after the taking of Fig. 12-B is seen to flow immediately into the colon without regurgitation up the ileum.

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## Roentgenologic Diagnosis of Diseases of the Small Intestine\*

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FOR more than twenty years examination with the roentgen ray has been an established and extraordinarily efficient method of diagnosing diseases of the esophagus, stomach, duodenum and colon, but during most of this period the small bowel beyond the duodenum seldom was subjected to thorough and systematic investigation. For the neglect of this field there seemed to be good and sufficient reasons; diseases of the jejunum and ileum are relatively rare, complete examination of the small bowel is time-con-

to identify many of them with precision. It is scarcely to be doubted that progress will continue and that eventually roentgenologic examination of the small bowel will become as diagnostically reliable as that of the stomach and colon.

A standardized technic of examination can hardly be prescribed, for examiners are likely to differ as to details, but one that has proved most satisfactory at The Mayo Clinic is as follows: The patient appears for examination in the morning after fasting over-

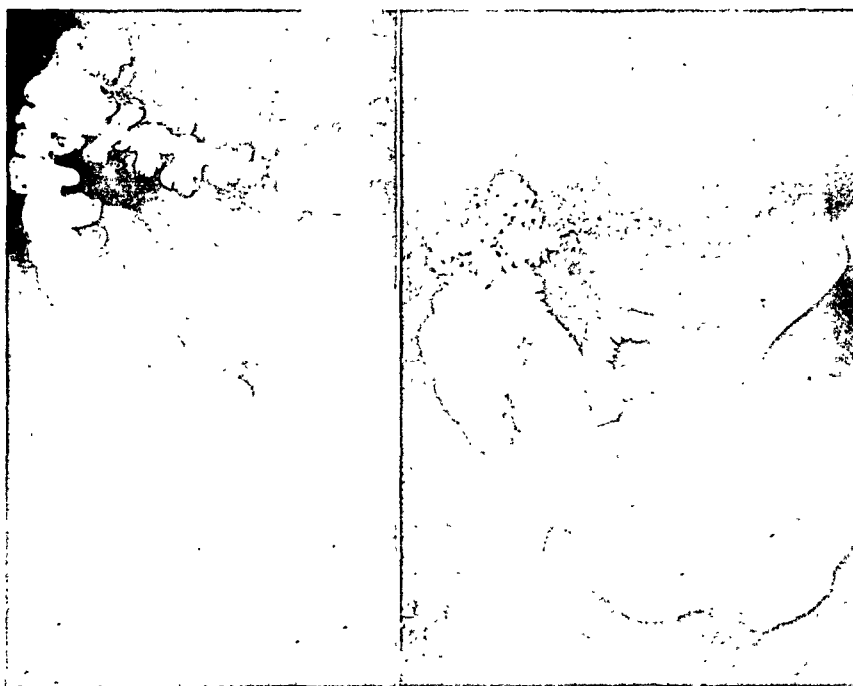


Fig. 1. *Left*, coils of lowermost ileum, the cecum, ascending colon and the hepatic flexure as seen with the opaque meal; *right*, the same segments as seen with the opaque enema.

suming, and diagnostic interpretation is rather difficult. Nevertheless, low incidence of disease in certain parts is not a valid excuse for failing to search for it, however difficult examination and diagnosis may be. Accordingly, in recent years the small bowel has been an object of more persevering study, and patient investigators have found it possible not only to disclose lesions that had hitherto escaped recognition but also

night. First a brief roentgenoscopic inspection is made in order to ascertain whether there are any signs of intestinal obstruction, for marked stenosis contraindicates administration of bariumized media. It is assumed also that the clinician is well aware of this contraindication and will co-operate with the radiologist in respecting it.

If no indications of obstruction are seen, the patient is required to drink 8 oz. (240 cc.) of a suspension of equal parts by volume of barium sulfate and water. After the usual inspection of the stomach and duo-

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denum the examiner tries by manipulation to force as much as possible of the suspension through the pylorus in order to obtain a more or less continuous column of the opaque medium. The length of the column will be limited according to the amount that the bowel will receive during the few minutes allotted to the session, but in its progress the mass, notwithstanding its tendency to become segmented, will exhibit the duodenum and upper coils of jejunum satisfactorily. Then the patient rests for a time, lying on his right side to favor further evacuation of the stomach. Roentgenoscopic inspection is repeated after ten or fifteen minutes, at which time a lower series of coils are likely to be depicted, and periodic examinations with rests

lated for inspection. They should be studied both before and after the enema is evacuated from the colon (Fig. 1). It should be unnecessary to say that examination of the small bowel is essentially a roentgenoscopic procedure, but roentgenograms often are desirable for permanent record or for leisurely study of petty or indefinite manifestations observed on the screen.

Important normal characteristics of the small bowel are its mobility and flexibility on manipulation, its distensibility by an advancing column of opaque medium, uniform caliber of any barium-filled segment, and smooth regularity of the luminal border, except for indentations produced by peristaltic contractions.

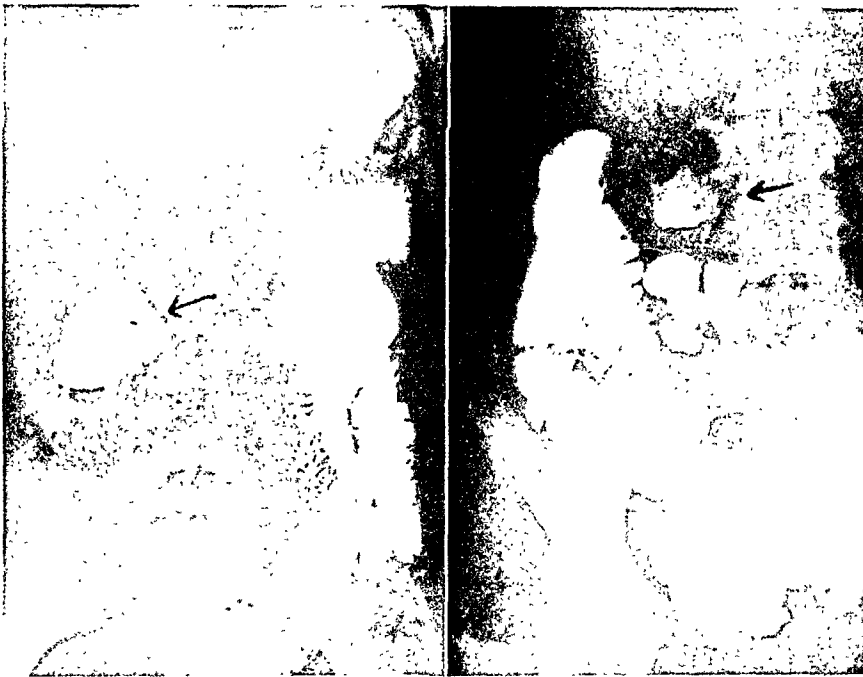


Fig. 2. *Left*, large diverticulum at the junction of the second and third portions of the duodenum (arrow); *right*, the same diverticulum twenty-four hours later. Meantime the patient had taken 2 oz. (60 cc.) of castor oil. The diverticulum contains a large residue of barium sulfate, gas and fluid. The roentgenogram was made after evacuation of the opaque enema.

between are continued until the stomach is practically empty.

At this stage forward movement of the suspension lags, and to stimulate activity the patient is instructed to eat breakfast of the kind to which he is accustomed. This renews functional activity and promotes the prime object of the technic which is to exhibit well filled coils successively throughout the bowel. After breakfast periodic inspections again are made until the barium enters the large bowel.

As a rule, inspection of the lower loops of ileum is hampered by their tendency to descend into the pelvis where they mingle together and are not accessible to manipulation and separation for individual scrutiny. Study of this part of the bowel is best effected by filling it retrogradely during examination of the colon with the opaque enema. By this procedure the terminal coils of ileum are kept out of the pelvis and can be manipu-

These contractions and other mixing movements tend to divide and subdivide the column of barium until it is broken up into detached flecks and the technic is designed to obtain complete filling of loops in order to depict luminal contours.

When made visible by a thin coating of the suspension, the internal relief, produced by the valvulae conniventes and delicate grooves and ridges of mucosa resulting from tonic contraction of the muscularis mucosae, varies widely in emphasis and design, not only in different persons but in the same person at different times. It will be remembered that the valvulae conniventes begin in the second portion of the duodenum, are large and numerous from that point on through the upper half of the jejunum, diminish from there to the middle of the ileum and almost disappear in the lower segments of the ileum. Normal patterns formed by the valvulae and finer mucosal

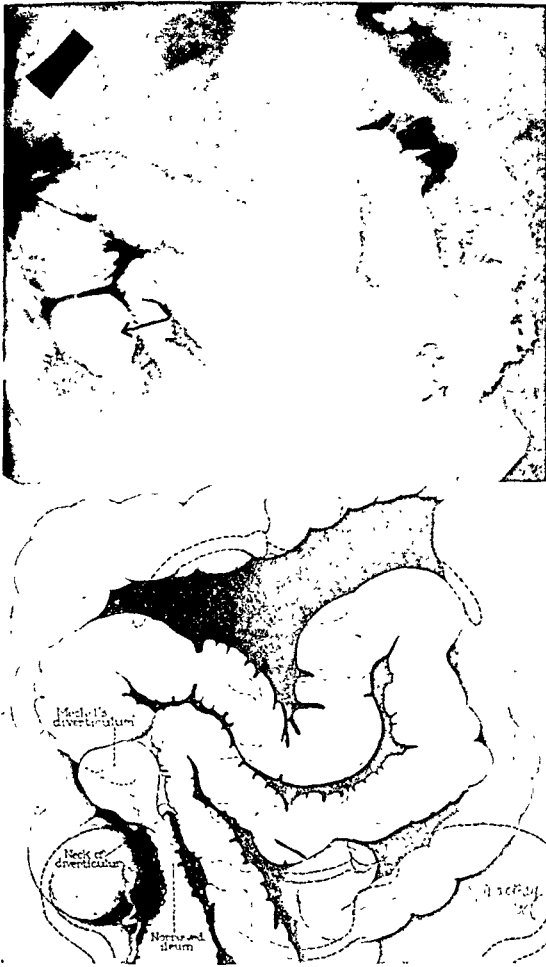


Fig. 3. Above, large Meckel's diverticulum (arrow); below, diagrammatic representation of the roentgenologic findings in the same case.

folds are so diverse that detailed description would be impracticable, but the existence of a definite pattern with repetitive designs is strong evidence that the internal relief of the segment under observation is normal. Wide latitude should be allowed in adjudging normal motility of the small bowel, for in apparently normal persons the suspension of barium may reach the cecum as early as forty-five minutes after leaving the stomach or as late as four or five hours after.

In the small bowel, as in other divisions of the alimentary canal, disease is manifested variously by deformity of the lumen, alternation of its caliber, stiffening of affected segments, signs of obstruction and changes in the internal relief. Irregularity, narrowing and broadening of the lumen are demonstrable in filled loops. Obstruction is shown by local accumulation of the suspension and dilatation of the bowel above the point of stenosis. Pathologic changes are evidenced also by disorder or effacement of the mucosal pattern. The character, extent, distribution, singleness or multiplicity and varying combinations of these signs enable diagnostic interpretations to be made.

Diverticula are of common occurrence in the duodenum, especially in the vicinity of the ampulla of Vater. When filled with barium the bulbous sacculations are readily demonstrable and scarcely mistakable. It is doubtful whether they ever give rise to symptoms or have any clinical significance, although the possibility that large filled diverticula may produce obstruction by pressure or that ulceration may result from prolonged retention cannot be excluded (Fig. 2). Diverticula of the jejunum are not often encountered. When present they are likely to be large and multiple. Filled sacs are easily recognizable and they may retain barium after the affected segment of bowel is empty. Ordinary diverticula of the ileum are rarest of all and usually small.

Meckel's diverticula are relatively common, for statistics indicate that they are found in 2 per cent of all persons, with a preponderance of 2 to 1 in males. This variety of diverticulum occurs only in the terminal 150 cm. of ileum and more often in the terminal 45 cm. The sacs vary widely in shape, position and size. Often they are small, but in one recorded instance the diverticulum was 66 cm. long. In many instances, perhaps a majority, Meckel's diverticulum is practically symptomless, but in other cases intestinal obstruction or hemorrhage may occur. A definite roentgenologic diagnosis of the condition can hardly be made without demonstration of the sac and its communication with the ileum by visualization with the opaque medium. So seldom has this been accomplished



Fig. 4. Obstructing annular carcinoma of the second portion of the duodenum (arrow). This illustrates the classic roentgenologic syndrome of intestinal carcinoma.

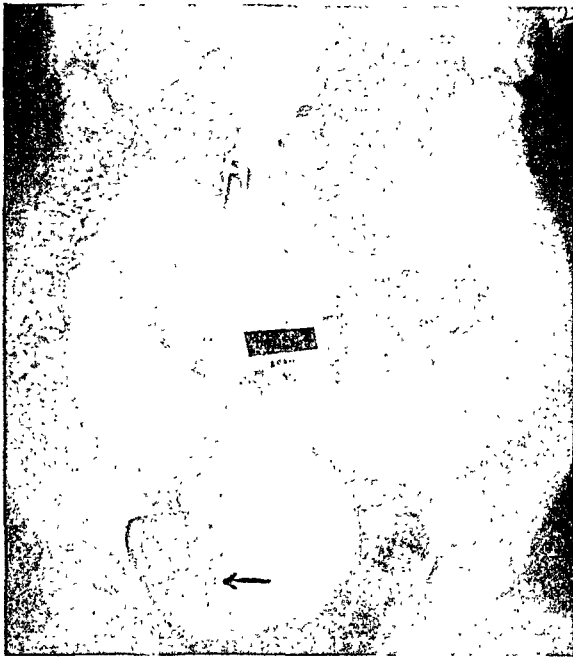


Fig. 5. Intussuscepting annular carcinoma low in the jejunum. Marked secondary dilatation of the intestine above the lesion.

that few pre-operative diagnoses, apparently less than a dozen, have been reported. However, even when conclusive evidence is lacking or not observed, there may be inflammatory narrowing of the ileum from extension of diverticulitis. If the narrowing is short it is likely to be attributed to an annular tumor; if long, to a hyperplastic ileitis alone (Fig. 3). But localized narrowing in the lower portion of the ileum, without other manifest abnormalities, should at least be considered as potentially due to Meckel's diverticulum, and thus the roentgenologic data may contribute substantially to a final correlated diagnosis.

New growths, whether benign or malignant, occur less often in the small bowel than in any other division of the alimentary canal. Their principal roentgenologic manifestations, like those of new growths elsewhere in the canal, include localized deformity of the lumen, a palpable tumor corresponding to the deformity, obliteration of mucosal markings at the site of the neoplasm, and signs of obstruction (Fig. 4). This, of course, is a dogmatic summary, for the signs vary as to their presence, combination and emphasis, and they are seldom complete and typical in a given case. Since ulceration of varying degree is a common characteristic of new growths, their gross appearance depends on the ratio between ulceration and tumefaction. Predominantly tumefactive lesions intrude into the lumen and produce corresponding defects in the shadow of the opaque medium; predominantly ulcerative lesions appear as marginal projections of the shadow. The palpability of a growth depends to some extent on the amount of tumefaction, but most of the small bowel is so readily accessible to palpation that even the extensively ulcerated growths can be felt. Destruction of mucosal markings in the area of the tumor is common, although the markings over

intramural growths may be preserved for a time.

Definite signs of obstruction, such as arrest of the medium and dilatation of the bowel above the point of stenosis, are seldom present, for as a rule only encircling growths that are not deeply ulcerated are capable of markedly obstructing the liquid intestinal content. Occasionally, however, any variety of tumor may give rise to intussusception and consequent obstruction (Fig. 5).

Benign new growths are exceedingly rare. More often they are single and, when multiple, not numerous. Usually they are small, pedunculated and not evidently obstructive. They are not subject to deep ulceration and thus the shadow-defects representing them are likely to be smoothly ovoid. Intramural myomas exhibit themselves as hemispherical shadow-defects, and the intramural situation of these tumors is apparent on palpation.

The extreme rarity of primary carcinoma of the duodenum is well known, but the disease is less rare in other parts of the small bowel. In most instances scirrhus carcinoma is rather easily disclosed and identified, for usually it encircles the bowel, ulceration is only superficial, the resulting shadow-defect is smooth and concentric, a corresponding mass can be felt, obstruction is evident, and the entire picture will scarcely be mistaken for that of any other lesion. Most of the malignant neoplasms of the small bowel, however, are soft mucoid carcinomas. When first dis-



Fig. 6. A stage in the examination of the small intestine illustrating a small, well-circumscribed area of ulceration (arrow) in the second portion of the duodenum associated with a sharply defined mass located by the examiner in the wall of the duodenum and for the most part in the submucous structures. At operation the lesion proved to be a leiomyoma.

covered they usually have sloughed so extensively that only a crateriform or deeply pitted base remains. The remnant of the tumor may or may not be palpable, and, almost without exception, signs of obstruction are lacking. If, despite sloughing, a considerable portion of the tumor remains, the diagnosis will be fairly obvious, but if the carcinoma has been destroyed to its base tuberculous or non-specific enteritis may have to be considered in the differential diagnosis. The fact that carcinoma commonly is limited to a short segment of bowel, whereas enteritis tends to affect relatively long segments, may aid in making the distinction.

Although sarcomas occur much less often than carcinomas, they constitute a substantial percentage of the malignant new growths. Most of those we have encountered at the clinic proved to be leiomyo-

manifestations comprise mural thickening, destruction of the mucosal relief and narrowing and shortening of the affected segment.

Thus, any attempt at roentgenologic distinction of one type from the other might seem hopeless. But, unless the picture is obscured by abscesses and fistulas, in which event efforts to make a differential diagnosis will almost certainly fail, the roentgenologic signs are often rather distinctive. In typical instances of tuberculous enteritis the luminal contour is roughly and irregularly corrugated. On the other hand, in typical instances of chronic nontuberculous enteritis the luminal contour, like that resulting from chronic ulcerative colitis, is smooth, and the narrowing is uniform (Fig. 7). In any case, however, final diagnosis should not be made until the presence or absence of tuberculous foci elsewhere has been determined. If

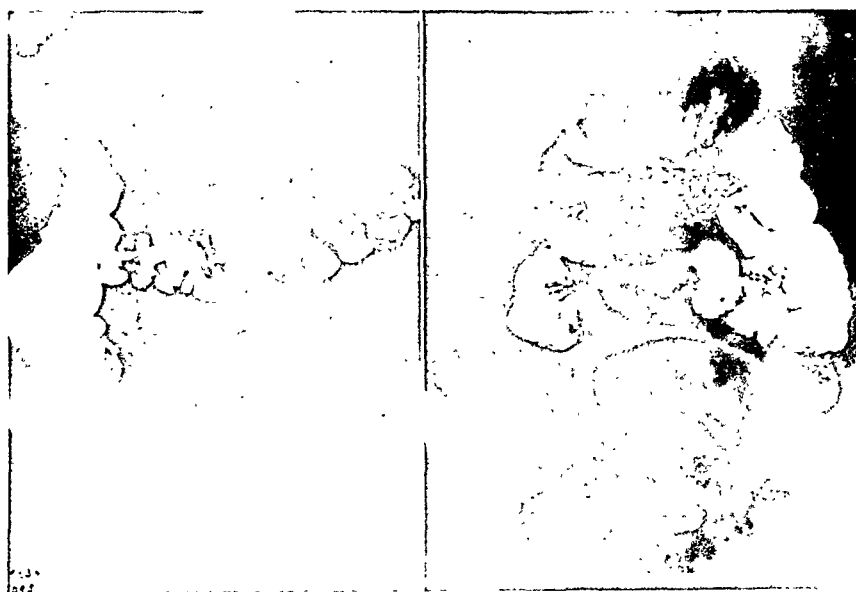


Fig. 7. *Left*, nontuberculous ileitis; *right*, tuberculous ileitis. The smooth contours of the nontuberculous form may be compared with the roughly corrugated, irregular narrowing produced by the tuberculous form.

sarcomas, and their roentgenologic appearance was similar to that of simple intramural myomas (Fig. 6).

Although chronic inflammatory disease of the small bowel may be caused by any of various micro-organisms or parasites, only tuberculous enteritis and enteritis of undetermined origin occur sufficiently often to be of practical interest. The symptoms, morbid anatomy and roentgenologic manifestations of these affections are so nearly alike that differential diagnosis is usually difficult and often impossible. Pathologically, both diseases are characterized by hyperplasia, ulceration and cicatrization in varying proportions, and abscesses and fistulas may complicate either variety. Either disease may be restricted to the small bowel, notwithstanding the fact that tuberculosis usually affects both small bowel and colon. It is not strange, therefore, that the two diseases can seldom be distinguished from each other by macroscopic inspection of affected tissues. In both types the roentgenologic

active pulmonary tuberculosis is found, the enteritis also is likely to be tuberculous. The existence of calcified mesenteric lymph nodes is suggestive that a case of enteritis is tuberculous. Results of tuberculin tests and examination of stools for tubercle bacilli may be helpful or decisive.

In certain nutritional deficiency states, such as pellagra, nontropical sprue, celiac disease in children, chronic alcoholism and pancreatic insufficiency, alterations in the roentgenologic appearance of the small bowel are often observed. These changes, though not identical in all the conditions named, are so nearly alike that reliable differential criteria have not as yet been established. Progress of the opaque medium through the bowel is markedly slowed, peristalsis is sluggish, the intestinal contents divide and subdivide irregularly, the mucosal relief may be either subdued or exaggerated, and contours of filled loops may be unusually smooth at one time and unusually rough at

another. A striking feature is the eccentric distribution of the medium, which forms dense accumulations in some of the intestinal loops and is diffusely dis-



Fig. 8. Well-circumscribed area of ulceration in the second portion of the duodenum (arrow) produced by carcinoma of the head of the pancreas.

persed in other segments of the bowel. It is noteworthy that the intensity of all these signs is in direct ratio to the intensity of the clinical manifestations.

Involvement of the small bowel by disease originating in adjacent structures is relatively common. New growths, especially those of the pancreas, mesentery or pelvic organs, sometimes invade the bowel directly or produce mucosal ulceration by pressure, and inflammatory affections, such as diverticulitis of the colon and salpingitis, sometimes implicate the intestine and deform its lumen (Fig. 8). Often it is difficult to distinguish extrinsic from intrinsic lesions, but when the process has arisen outside the bowel, the intestinal mucosa with its characteristic markings is likely to be preserved, and even when mucosal ulceration has ensued the extent of destruction is not likely to be proportionate to the size of the lesion as revealed by palpation.

From this summary it will be evident that the roentgenologic differential diagnosis of lesions of the small bowel is not yet as accurate as that of lesions of the stomach and colon, and that an unusual amount of consideration must be given to clinical data in arriving at a final opinion. This can be accounted for, not only by the difficulty of satisfactorily examining the long and slender bowel, but also by the fact that the experience of individual examiners is still relatively scant. It is highly probable that an enlargement of their experience, by more frequent demands for this examination, will result in the discovery and specific identification of many lesions of the small bowel that are now eluding diagnosis.

## Changes in the Small Intestine Associated With Deficiency Disease

By

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and

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**A**BNORMALITIES of the small intestine demonstrable by X-ray indicative of functional rather than organic change were first reported by one of us (1) and by Snell and Camp (2). These were observed in cases of idiopathic steatorrhoea, or non-tropical sprue. Subsequently we noted similar changes in a group of cases of chronic ulcerative colitis complicated by deficiency disease (3) and in tropical sprue (4).

These abnormalities are constantly present in cases presenting the clinical phenomena of advanced deficiency disease. In milder cases the parallelism is not exact. In sprue it was noted that the intensity and the extent of the changes varied directly with the severity of the disease (4, 5) and that regression occurred under adequate specific therapy. Likewise in the cases of chronic ulcerative colitis roentgenologic examination proved to be of some prognostic value in that it afforded an indication of the efficacy of treatment directed against the deficiency state.

The changes are characteristic. They are most

commonly demonstrable in the duodenum and the jejunum but may be evident throughout the entire length of the small intestine. The mucosal markings are coarser than normal. There is striking variation in the contour and size of the lumen and abnormal collections of gas may be present. The normal motor activity is disturbed, frequently producing a segmented distribution of the barium in dilated and isolated coils. The opaque meal usually passes through the jejunum slowly and irregularly. The filled areas show no evidence of peristalsis. At times all of the barium which has left the stomach is collected in a localized segment while the remainder of the jejunum and the duodenum are empty. Gastric emptying is irregular corresponding apparently to the delay in the forward progress of the opaque meal through the small intestine. Although the rate of passage of the barium through the small intestine is subject to wide variation, the forward progress of the opaque meal is not more rapid than normal. A twenty-four hour

residue in the cecum and ascending colon is not uncommon.

The association of these changes with clinically obvious deficiency disease complicating ulcerative colitis, and their invariable presence in active sprue strongly suggest that they contribute to the deficiency state by interference with absorption, and thus tend to produce a vicious ascending spiral. There is significant evidence to support this concept. Defective absorption from the intestine has been proven in sprue. Examination of the feces reveals a large excess of fatty acids. Large amounts of liver extract given by mouth are frequently ineffective, whereas parenteral administration of much smaller amounts of the same preparation is followed by dramatic improvement (6). There is an abnormally small rise of blood sugar following the ingestion of glucose by mouth (7). After intravenous administration, however, a normal blood sugar curve is obtained. Direct measurement of the rate of glucose absorption from the small intestine using an occluding balloon apparatus has demonstrated a reduced rate of absorption (8).

There is similar evidence to indicate that defective absorption constitutes the conditioning factor in the development of deficiency disease associated with chronic ulcerative colitis. This complication occurs in a considerable proportion of cases (9). It has been observed to develop in the course of hospitalization and despite sufficient and adequate diet. Direct measurement of glucose absorption in this disease has likewise revealed a definite absorption defect (8).

Clinical and experimental evidence indicates that the factor of defective absorption is operative in other types of deficiency. The resistance of certain cases of pernicious anemia to oral liver extract therapy is suggestive. Impaired absorption of glucose from the intestine has been demonstrated in untreated pernicious anemia, and in alcoholic polyneuritis complicated by pellagra. Adequate treatment was followed by restoration of the absorption rate to normal (8). It has likewise been shown that the absorption of potassium iodide may be greatly delayed in deficiency states (10).

The mechanism responsible for the roentgenologic changes in the small intestine observed in the mixed deficiency states and in sprue has not been demonstrated. Microscopic examination of material obtained from a limited number of cases has revealed no significant anatomic change. One of us (3), however, has previously suggested that they may represent some degree of edema of the mucosa, together with functional impairment of motor activity and of tonus of the intestinal musculature. Jones (11) has shown that free fluid accumulates in the serous cavities, and a striking increase in the water content of the viscera occurs when animals are subjected to varying degrees of protein starvation. He points out that such changes imply marked alteration of tissue physiology which are inconsistent with normal function. Barden and his associates (12) have shown that reduction in the concentration of the serum proteins of the dog by plasmaphoresis is accompanied by roentgenologic changes in the small intestine. There is retardation of the passage of a barium-water meal and the intestinal pattern is altered. Both of these abnormalities are corrected by restoration of the serum proteins to normal levels. Examination of the X-ray films

published in their article reveals changes which are very similar to those observed in deficiency states and in sprue in man.

Abnormalities of the intestinal tract have likewise been noted in experimental avitaminosis in animals. Gross (13) observed reduced motor activity in rats shortly after the withdrawal of Vitamin B<sub>1</sub> from the diet. Plummer (14) reported that deficiency of this vitamin reduced the tone of the intestinal musculature, and the amplitude, the rate, and the length of time during which spontaneous contractions of an isolated segment occur. Rose, Stucky and Cowgill (15) observed diminished gastric motor activity in dogs subjected to this deficiency. Clinical disorders of the gastro-intestinal tract in man, functional in nature have been shown frequently to be related to insufficient supply of the Vitamin B complex (16).

### MATERIAL AND METHODS

Detailed roentgenologic studies of the small intestine have been made of twenty-eight individuals using the technique and criteria previously described (3). The clinical diagnoses are listed in Table I. Nine of

TABLE I  
*Clinical conditions*

Total individuals studied	28
Ulcerative colitis . . . 19	Heitis . . . . . 1
Neurosis . . . . . 4	Polyposis of rectum . . 1
Amebiasis . . . . . 1	Normal control . . . . 2

these have presented no abnormalities. The remaining 19 show to a greater or less degree the characteristic changes which accompany deficiency disease. All have been studied to determine the incidence and type of avitaminosis; by analysis of symptoms, physical signs, and blood levels of carotene, Vitamin A, and ascorbic acid. We have previously reported the methods and normal standards for the latter (17). Observations have likewise been made of gastric acidity, gastric emptying time, small intestine motor rate, food allergy by the test diet technique, anemia, and the levels of the plasma proteins and chloride.

### FINDINGS

With two exceptions, the nine individuals having normal small intestine roentgenologic findings presented no evidence of avitaminosis by symptoms, physical signs, or blood vitamin assay. One case of chronic ulcerative colitis had a subacute scurvy and a moderate Vitamin K deficiency; a second showed low levels of carotene and Vitamin A. Three had a proven gastro-intestinal food allergy and two others were suspect. Definite hypoacidity after histamine stimulation was present in two, and four were moderately anemic. The plasma proteins and chloride were not determined in this group.

The characteristic abnormal mucosal pattern was demonstrable in each of the nineteen cases presenting small intestine changes. Twelve of these exhibited clinical indications of Vitamin B complex deficiency. Blood vitamin assay gave low values for ascorbic acid in six, Vitamin A in two and carotene in one. Proven food allergy existed in five and was absent in the re-

mainder. Six had hypo or anacidity and eight were normal. Hypochromic anemia was present in thirteen, a macrocytic anemia in one, and two had normal blood findings. The plasma protein values were normal in seven and low in two of the group. Similarly, the chlorides were normal in five and low in three.

Seventeen individuals presented segmentation of the barium column in the small intestine. Ten of them revealed clinical indications of Vitamin B complex deficiency. Blood vitamin assay gave low values for ascorbic acid in five, and Vitamin A in two. The carotene content was normal in all. Food allergy was demonstrated in five, and was absent in the remainder. Four individuals had hypo or anacidity; and eight had normal values. Anemia of varying degree was present in thirteen. The plasma protein levels were normal in seven and low in two. The chloride values were normal in five and low in three.

Dilatation of individual coils or groups of coils of small intestine were present in ten of the cases. Seven of these presented clinical evidence of a Vitamin B complex deficiency. Vitamin assay revealed low levels of ascorbic acid in four, and of Vitamin A in one. The carotene values were normal. Four individuals had a

the presence of the small intestine abnormalities and evidence of avitaminosis. One individual in the normal group presented the clinical picture of subacute scurvy which was confirmed by the laboratory, and one was found to have low values for blood carotene and Vitamin A. No other evidence of vitamin deficiency was demonstrable.

Fifteen of the nineteen cases presenting small intestine changes, however, yielded clinical or laboratory evidence of avitaminosis. Furthermore the types of deficiency encountered would appear to be significant. Indications of lack of the Vitamin B complex were noted in twelve of the fifteen individuals. Low levels of blood ascorbic acid although not uncommon, were observed much less frequently. Low levels of carotene and blood Vitamin A were infrequent.

The Vitamin B complex at the present time is recognized to comprise four substances essential for man, thiamin or Vitamin B<sub>1</sub>, riboflavin, nicotinic acid, and Vitamin B<sub>6</sub>. Since satisfactory methods for the quantitative estimation of these substances have not been available, evidence of B complex deficiency must be based upon the clinical criteria generally accepted as indicative of deficiencies of these factors. In view

TABLE II  
*Avitaminosis and small intestine changes*

X-ray Changes	No. Cases Total: 23	Incidence Avitaminosis	Clinical Evidence of Avitaminosis	Evidence of B. Complex Deficiency	Low Assay	Type of Deficiency Vitamin Assay
Absent	9 cases	2 cases	1 case	0 cases	2 cases	C & K — 1 case A, Carotene 1 case
Mucosal Changes	19 "	15 "	12 cases	12 "	8 "	C — 6 A — 2 Carotene — 1
Segmentation	17 "	15 "	10 "	10 "	7 "	C — 5 A — 2
Dilatation	10 "	8 "	7 "	7 "	5 "	C — 4 A — 1

definite food allergy. The remaining six gave no evidence of this condition. Three had a normal gastric acid curve, four had hypo or anacidity. Anemia was present in eight. The plasma protein values were normal in five and low in two. The chloride levels were normal in four and low in three. Serial films did not reveal hypermotility of the small intestine or an increased rate of progress of the barium meal.

### DISCUSSION

The studies of these twenty-eight cases have failed to reveal a significant correlation between the presence of the small intestine abnormalities demonstrable by roentgenologic examination, and the levels of the plasma proteins or chloride, the presence or absence of gastric hypo or anacidity, or the concomitant existence of demonstrable gastro-intestinal food allergy. Anemia, in all but one case hypochromic in type, was commonly observed in the abnormal group. Certain of these individuals, however, gave no evidence of a blood dyscrasia, and four of the group in whom the radiologic changes were absent had comparable grades and types of anemia. We have previously pointed out that evidence does not support the possibility that these small intestine changes represent the local effect of the action of bacteria or bacterial products (3).

There is, however, a striking correlation between

of the experimental data cited above, of the relationship between B complex deficiencies and functional clinical disorders of the gastro-intestinal tract, and the high incidence of signs of B complex deficiency in association with the small intestine changes in this group of cases, it seems probable that the roentgenologic abnormalities of the small intestine demonstrable in unclassified mixed deficiency states, in idiopathic steatorrhea, and in sprue, are the expression of an insufficient supply of the Vitamin B complex. Additional correlative evidence may be cited. We have previously shown that these changes regress under intensive therapy with a crude liver extract, a rich source of the B complex (4). It is well known that depletion of stores of the water soluble vitamins occurs rapidly in the presence of insufficient intake. The higher incidence of ascorbic acid deficiency than of Vitamin A deficiency indicates also that this group of cases were deficient in certain of the water-soluble constituents of the normally protective diet. It is likewise probable that these changes in the small intestine once established contribute to progression of the deficiency state by impairment of the absorptive function.

Final evaluation of the role of the Vitamin B complex must await the development of satisfactory

quantitative techniques for the estimation of these substances.

## CONCLUSIONS

1. There is a definite correlation between the incidence of the small intestine roentgenologic changes characteristic of deficiency disease, and indications of avitaminosis.

2. It is probable that lack of the Vitamin B complex is responsible for the development of these changes.

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## DISCUSSION

DR. MAURICE FELDMAN (Baltimore, Md.): Drs. Kirklin and Weber have covered much of the ground on what is generally known regarding the radiologic investigation of the small intestine. Owing to the many technical difficulties encountered in small bowel roentgenography, it was formerly thought that very little information was derived by such a study, however, in recent years, since greater attention is being paid to small intestinal pathology, we have been able to detect lesions with greater ease and at an earlier stage.

It must be pointed out that the known radiologic signs as emphasized by the authors are late manifestations, and though it formerly seemed impossible to demonstrate the early signs, I believe that with meticulous care the early findings may be brought out with greater clarity.

I have been greatly interested in the observation of the early roentgen signs of small intestinal pathology as manifested by the mucosal changes. Since almost all of the roentgen literature presents only late findings, I had hoped that Drs. Kirklin and Weber would have told us something about the earlier manifestations; for instance, those that occur in early ileitis, in early carcinoma of the small intestine, and in deficiency diseases. Little mention is made of these conditions in the early stages.

I have been particularly interested in the appearance of the small intestine in deficiency diseases. At the Sinai Hospital of Baltimore, recently we have had occasion to study a case of deficiency disease presenting a marked

diarrhea. The jejunum in this case presented a narrowing of the lumen with a spiking or saw-tooth appearance of the mucosal contour. The picture was quite characteristic of pathology. On intensive Vitamin B therapy, the spiking mucosal picture as well as the diarrhea, had disappeared. I am presenting this roentgen picture as a possible early manifestation of vitamin deficiency disease.

Three slides are presented to show the case mentioned.

First, a close-up picture showing the spiking of the small intestine contour and throughout most of the jejunum one can observe signs that indicate spiking or saw-tooth appearance.

The second slide demonstrates the saw-tooth appearance much more clearly throughout the jejunum. In five hours there is a marked segmentation of the ileum, a picture simulating sprue, but clinically, as far as we could determine, the patient did not present any evidence of sprue. The third slide, two months later, following intensive Vitamin B deficiency therapy, the spiking of the bowel had disappeared, but there was some dilatation of the upper jejunum. However, in the five hours examination, after the Vitamin B therapy, the marked segmentation and marked stasis in the small intestine had entirely disappeared, and the motility was almost normal. There was a marked difference in the appearance of the small intestine between the two examinations in the two-month period of treatment.

DR. JOHN L. KANTOR (New York City): Mr. Chairman and Members: The small intestine is the engine room of the digestive tract, and it is encouraging to note the rapid progress that is being made in this very important field at the present time.

I believe that Dr. McGee did not make any lipase studies in his observations. One would like to know what the lipase is like in the small intestine because it seems possible to cut off the pancreas with its source of lipase and still have a reasonably adequate fat digestion. This was shown in surgical operations on human beings by Dr. Allen O. Whipple of New York, who demonstrated 80 to 85% fat digestion after resection of the head of the pancreas.

Then again, there is a widespread tendency to speak of all these conditions as deficiency states. However, it doesn't necessarily follow that the people who are the victims of what has been described have not been eating as many vitamins as anyone else. I think we should differentiate between deficiency states and conditions of deficient intestinal absorption. For example, idiopathic steatorrhea is primarily a disease of deficient absorption.

Also, I believe it has been stated that mucosal changes may be completely reversed, that they are reversible when the proper vitamins are given. However, this is not always true either. I had occasion to report a case of idiopathic steatorrhea in the May, 1940, number of the Archives of Internal Medicine, where the obliteration of the mucosal pattern of the jejunum was not reversed, and we secured the autopsy proof whereby the "permanent" nature of the change was confirmed. It is thus possible that the minor cases may indeed be functional and reversible, but there may well come about a change to an organic type wherein the mucosal changes are not entirely functional nor are they always entirely reversible.

DR. EVERETT D. KIEFER (Boston, Mass.): A purely functional disorder of the small intestine is difficult to establish on sound laboratory and X-ray grounds, yet there is no doubt but that the small intestine plays an important part in functional gastro-intestinal disorders, not only those due to nervous disorders but those due to irritative disorders resulting from improper diet, alcohol, or drugs.

Dr. Ingelfinger and Dr. Abbott have described a method which promises to give us a better insight into the abnormal and normal function of this part of the gastro-



intestinal tract; however, it may not be practical to intubate all patients who come to us with vague digestive disorders, and it is, therefore, necessary for the clinician to be on the lookout for factors in the history or in the routine X-ray examination, to establish which patients should have more study of their small intestine.

We have been interested in observing some of the subjective sensations experienced by patients who have had subtotal or total gastrectomy, as an indication of some of the symptoms that might arise from the effect of food in the small intestine.

The symptoms which seem to be most common are, first, extreme epigastric fullness immediately after eating. Other patients describe the sensation as a hungry, gnawing sensation which they experience soon after eating. Then there are vasomotor disturbances which seem to be reflex results from rapid filling of the small intestine. Sweating is often a prominent symptom.

There are other clinical symptoms and signs. Owles, in Hearst's clinic, has described excessive flatulence and even diarrhea which he believes are due purely to hypermotility of the small intestine interfering with the proper digestion and absorption of carbohydrates, and allowing for fermentation with acid and gas formation in the colon.

In the X-ray studies the changes in the motility and changes in the small intestine pattern can be watched for. Hypermotility is more apparent than hypomotility.

(Slide) This slide was taken two and a half hours after a regular barium meal, and shows the excessive motility. The head of the meal has passed much farther along than ordinarily and the segmentation and changes in the small intestine are seen which often go with small intestine irritability. This condition was caused by the excessive use of cathartics.

We have found it practical in our routine examination to take a film two to three hours after the barium meal, because it helps us to pick up suggestive signs of both functional and organic small intestinal disorders.

DR. HENRY A. RAFSKY (New York City): In 1933, Cole, before this Association emphasized the use of the water and barium meals in comparatively small amounts, with the X-rays taken at frequent intervals, to locate lesions of the small bowels. Dr. Pickhardt and I have been interested in this subject for the last few years, in an attempt to solve some of our so-called problem cases, which run the gamut of investigations and repeated X-ray examinations. Some of these patients even have their appendices removed before the lesion is finally diagnosed. As Dr. Kirklin stated, everybody uses his own modification in the diagnosis of small intestinal lesions. I would like to show three slides to illustrate how you can locate definite pathology by this method, whereas the usual routine examinations did not reveal it.

(Slide) This patient had periodic attacks of pain in the right lower quadrant for four years. A diagnosis of appendicitis had been made. The routine examination did not reveal anything abnormal. A small intestinal study was made and here you can see that while the appendix is visible, there is also present a polyposis of the terminal ileum and as you will see in the next slide, diverticuli of the cecum. The third slide is shown to emphasize the fact that if, in the chronic case, the small intestinal studies are conducted just before the acute attack has subsided, you will often be rewarded with definite information, which was not obtained upon a previous examination. This patient suffered periodic attacks of pain in the right lower

quadrant for twenty years. His appendix was removed but the attacks still continued. Six months before we examined him, by means of a small intestinal series, a thorough routine X-ray examination had been made, and was reported essentially negative. We had an opportunity to study the patient just before one of his acute attacks had subsided. X-ray films were taken every two hours. Here, as you see in the four hour film there is a stoppage at the ileo-cecal valve and in the eight hour film you can observe small loops of bowel in the cecum. For the first time in twenty years a diagnosis could be made, which in view of what is seen in the films, was relatively simple, namely that the patient had an intussusception. The patient was operated upon and the underlying cause for the chronic attacks of intussusception was a papilloma of the cecum. I also wish to say that at times we supplement these examinations with compression studies and these investigations often help us in making a differentiation between a spastic affection and an organic lesion. In regard to deficiency disease we must bear in mind that in treating these patients with diarrhea the question often arises as to how much benefit these patients derive from vitamins given by mouth. In ulcerative colitis, when sulphanilamide is given in as large a dose as five grams daily, per os, we rarely find more than two to three milligrams of sulphanilamide in the blood. This lack of absorption and utilization will most likely also apply to vitamin intake in this type of case. Therefore to overcome this lack of absorption and utilization, in these cases, the vitamins should be given parenterally.

DR. HEINRICH NECHELES (Chicago, Ill.): I should like to call Dr. McGee's attention to ferment estimation. It is important what time interval we use in determining proteolytic ferments. There are two-hour intervals, two, four, six, eight, ten, up to twenty-four, and these here (drawing on the board), are the units of ferment from titration or colorimetric determinations, and so forth.

Then we usually obtain a curve, or practically always, which runs like this, and in order to get a true expression of the quantity of ferments, we must use this time interval. If we go beyond this time interval, then larger as well as smaller amounts of ferments will yield the same values.

I know that Dr. McGee has used the twenty-four-hour interval, and I am afraid in a number of them he has lost the differences.

DR. LEMUEL C. MCGEE (Boston, Mass., closing the discussion): The observation made by Dr. Kantor that lipase would be an interesting study is very true. We were limited by our technical assistance. There are many, many aspects of the intestinal fluid which should be studied, and will be studied in the next few years by individuals using the Miller-Abbott tube for intestinal intubation.

As to the proteolytic method, I am aware of the curve which Dr. Necheles illustrated, in enzyme studies and, as a matter of fact, the limitations of all methods in enzyme studies, once the fluid is withdrawn from the gastro-intestinal tract and we assign to them a certain pH for their study. We have a mixture of proteolytic enzymes here and at best we can only assume we get an indication of the direction of the drift. The method used was that of Owles, inasmuch as he made the first description of the method of using the isolated segments for enzyme study. We wished to compare his results with our own and adopted his methods for that reason.

## Further Observations on the Clinical Use of Vitamin K\*

By

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**D**URING the last year four important developments have occurred in our knowledge of Vitamin K. These are: (1) isolation and identification of the naturally occurring forms of the Vitamin ( $K_1$  and  $K_2$ ); (2) recognition of the antihemorrhagic properties of a number of related naphthoquinones; (3) observation that various conditions besides hepatic and biliary disease may give rise to hypoprothrombinemia and (4) demonstration of the fact that the liver is the chief and probably the only site for the manufacture of prothrombin.

If deficiency of Vitamin K may be defined tentatively as a condition associated with actual or latent hemorrhagic manifestations and characterized by prolonged prothrombin clotting time or diminished quantity of prothrombin in the blood, three questions of a clinical nature can be answered readily; namely, 1. How common is Vitamin K deficiency? 2. Under what circumstances does it occur? 3. How successfully can the condition be treated? States of vitamin deficiency corresponding to this description are encountered commonly in connection with certain gastrointestinal disorders, the general nature of which suggests that deficient absorption of Vitamin K from the intestinal tract is the one factor common to the group. Vitamin K deficiency of this type is readily amenable to treatment with various extracts that contain the vitamin or with certain quinoid compounds.

It is our purpose in this paper to present some observations on hypoprothrombinemia associated with hepatic and cholelith disease but unassociated with obstruction of bile ducts and associated with certain conditions of the intestine and deficiency states. The responses obtained from several synthetic compounds that have antihemorrhagic properties will also be considered together with a comparison of these substances, their rate of action and the occasional failures which have been observed when these compounds have been employed.

The story of Vitamin K deficiency and hypoprothrombinemia associated with obstructive jaundice has been told too often to bear repetition. It suffices to say that for human beings exclusion of bile from the intestine, either by obstruction of the common duct or by means of a complete external fistula, will lead rapidly to deficiency of prothrombin and to serious hemorrhage. The latent hemorrhagic tendency of such patients is precipitated all too frequently by surgical procedures designed to restore the continuity of the biliary passages. There appears to be some evidence which indicates that the degree of hepatic damage produced by biliary obstruction may be a

determining factor in the precipitation of hemorrhage. The administration of bile alone will correct the hemorrhagic state in cases in which bile is excluded from the intestine, provided that the diet is adequate. However, the giving of bile plus concentrates of Vitamin K or the parenteral administration of certain compounds of naphthoquinone is much more rapidly effective. This fact is now recognized so generally and treatment is so well standardized that so-called cholemic bleeding has become decidedly uncommon. So far as the danger of bleeding after operations on the biliary tract is concerned, difficulties now arise chiefly in cases in which jaundice is not present but in which severe degrees of cholelith and biliary infection are. In such cases, the danger of post-operative hypoprothrombinemia has not been generally appreciated.

As the results of studies on mammals other than man indicate, dietary deficiency in respect to the usual sources of Vitamin K is of itself rarely productive of hypoprothrombinemia in man. If a "toxic" factor is added, deficiency of prothrombin may develop. In Kark and Lozner's (1) cases the degree of depletion of prothrombin was not great and the tendency toward bleeding was clearly due to scurvy. These authors used a modification of Quick's method and thus determined the clotting time after they made a series of dilutions of the plasma to be tested. We recently have observed another patient who subsisted for two years on a virtually fat-free diet in which leafy vegetables and other known sources of Vitamin K were practically excluded; this patient had only a minor degree of hypoprothrombinemia of about the same order of magnitude as in the group reported by Kark and Lozner. A number of patients with anorexia nervosa and nervous vomiting have been studied and do not have a striking deficiency of prothrombin in the plasma. A previously deficient diet, continued vomiting, or diarrhea, however, may lay the groundwork for a deficiency state in respect to Vitamin K but some other incident, such as an abdominal operation may be required for its precipitation. Table I and Fig. 1 represent the findings and results of treatment in one such case. The patient was a man who underwent partial gastrectomy for gastrojejunal ulcer. Although the deficiency of prothrombin was mild, it was definite and appeared somewhat more prominently in the diluted specimens of plasma than was otherwise apparent.

Hypoprothrombinemia and the hemorrhagic diathesis have been demonstrated in a large number of gastro-intestinal diseases, including sprue, intestinal polyposis, regional ileitis, intestinal obstruction, gastrocolic fistula, pyloric obstruction and ulcerative colitis. In such cases, the combination of a deficient

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diet, loss of essential substances by vomiting and diarrhea and an abnormal state of the mucosal surface of the gastro-intestinal canal is sufficient to produce serious depletion of prothrombin. As in cases of jaundice, the deficiency does not often reach serious proportions until after the performance of some surgical procedure designed to correct the primary

TABLE I

PROTHROMBIN TIME (IN SECONDS) AS DETERMINED BY MAKING A SERIES OF DILUTIONS OF UNKNOWN PLASMA WITH PROTHROMBIN-FREE PLASMA, FOR A PATIENT WHO UNDERWENT GASTRIC RESECTION AND THE EFFECTS OF TREATMENT WITH VITAMIN K<sub>5</sub>

UNKNOWN PLASMA IN SAMPLE, PER CENT	POSTOPERATIVE DAYS				
	FIRST*	THIRD	FIFTH	SEVENTH	EIGHTH
100	20†	26	28	34‡	26
80	20	30	32	42	30
60	25	36	40	53	35
40	29	45	58	80	45
20	52	85	106	150	75

\*DAY OF OPERATION.

†SPECIMEN OF BLOOD TAKEN JUST BEFORE OPERATION WAS PERFORMED.

‡2 MG. OF VITAMIN K<sub>5</sub> GIVEN INTRAVENOUSLY.

condition. This fact naturally raises the question of the mechanism involved in cases of post-operative Vitamin K deficiency. Clinicians generally are inclined to blame the factors of anesthesia and anoxia because of their known potential effects on the liver. The matter of trauma to viscera also has been brought into the foreground by the recent studies of Lord (2) who showed that simple manipulation of the liver of the anesthetized dog reduced the level of prothrombin in plasma. Finally, the practice of repeated gastric lavage or continuous aspiration of the intestinal content, so often necessary in the post-operative management of patients who are seriously ill, seems to have a definite tendency to deplete the bodily stores of prothrombin, presumably by removing the coagulation vitamin from the intestine. It is important to note that other demonstrable vitamin deficiencies rarely develop in such cases and that administration of Vitamin K or related compounds effects a speedy correction of the condition.

Whatever the mechanism involved in the deficiency of Vitamin K in such cases may prove to be eventually, surgeons and clinicians have learned to follow the prothrombin coagulation time closely in all cases of previous biliary obstruction or infection, in cases of abnormality of the intestinal mucosa or of interference with the continuity of the gastro-intestinal tract and in cases in which the post-operative condition requires continuous aspiration of gastric or intestinal content. This practice has solved the mystery of obscure intestinal bleeding which occurred frequently in such cases and definitely has reduced post-operative morbidity and mortality.

Certain other observations also seem worthy of note: 1. Vitamin K or some compound with similar

antihemorrhagic activity probably is formed in the gastro-intestinal tract; this is an exception to the general rule that the organism cannot elaborate vitamins. From what is known of the antihemorrhagic activity of certain products of bacterial growth some of the material may be assumed to be a product of bacterial action. 2. There is little or no storage of Vitamin K in the body, as has been demonstrated experimentally by Greaves (3, 4) and by numerous clinical observers. Fatal hypoprothrombinemia has been known to develop in a far shorter time (one week or less) than that required for the development of other vitamin deficiencies.

#### EFFECTS OF TREATMENT OF PROTHROMBIN DEFICIENCIES WITH SYNTHETIC SUBSTANCES THAT HAVE ANTIHEMORRHAGIC ACTIVITY

In the earlier period of investigation of Vitamin K, therapy was handicapped by the lack of a suitable preparation of Vitamin K for intramuscular or intravenous administration. However, when the quinoid structure of Vitamin K was recognized and the antihemorrhagic properties of various naphthoquinones were recognized experimentally, several compounds that could be used intravenously became available for clinical trial. These bear approximately the same relation to Vitamin K concentrates as thyroxin does to thyroid extract; an exact dosage is possible and parenteral administration is facilitated. From the clinic have come reports of the use of phthiocol (5), 1,4-dihydroxy-2-methyl-3-naphthaldehyde and 2-

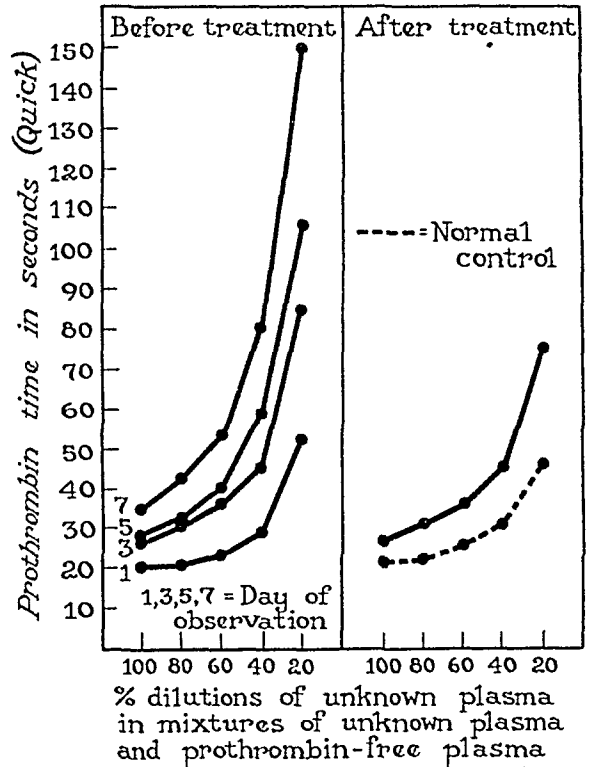


Fig. 1. Prothrombin time as determined by means of a series of dilutions for a patient who underwent gastric resection, and the effects of treatment with Vitamin K.

methyl-1,4-naphthoquinone (6) in various types of clinical cases.

The antihemorrhagic effects of these compounds were eminently satisfactory. Phthiocol was administered in doses of 25 to 50 mg. intravenously to nine of a series of ten patients. No irritation or reaction was noted. The delayed prothrombin time was corrected and bleeding in one case was controlled. The "naphthaldehyde" compound (1,4-dihydroxy-2-methyl-3-naphthaldehyde) which was kindly supplied to us by Dr. Doisy was given intravenously in another group of ten cases in doses of 10 to 20 mg. without reaction or irritation and with similar satisfactory results except in two cases of cirrhosis. The preparation, 2-methyl-1,4-naphthoquinone, was administered in a series of twenty cases. Orally, it was given in tablets of 1, 2, 3 and 5 mg. No untoward reactions were noted.

rach and Chance (10) have used this compound intramuscularly suspended in corn oil with very satisfactory results.

During the past few months, we have been giving another compound clinical trial, Vitamin K<sub>2</sub> (4-amino-2-methyl-naphthol hydrochloride) supplied by Parke, Davis and Company and are presenting our findings herein. This is a soluble compound, suitable for intravenous administration. It has been given in forty-five cases, composed of twenty-six cases of jaundice (including two with external biliary fistula), six cases of cirrhosis and thirteen cases of gastro-intestinal and miscellaneous lesions. In six of the cases of obstructive jaundice, in which a prolonged prothrombin clotting time was encountered, this defect was readily controlled. Bleeding was encountered in one case and was controlled. Also in one case of severe disease of

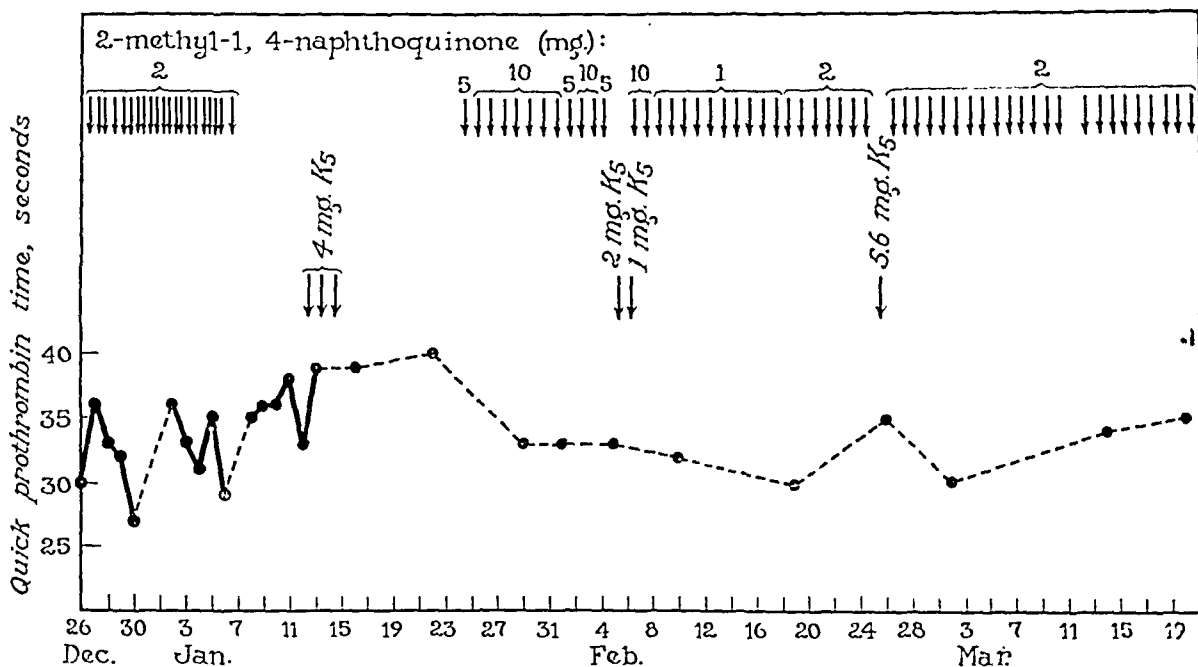


Fig. 2. Lack of response to naphthoquinones in a case of cirrhosis.

In most instances the elevated prothrombin clotting time returned to normal within twelve, twenty-four or thirty-six hours following the administration of the compound. This compound is not water-soluble in its original form but suspensions were found to be physiologically active. In other cases, a soluble salt of this compound, 2-methyl-1,4-naphthohydroquinone-sodium sulfonate was given intravenously in doses equivalent to 2 mg. of 2-methyl-1,4-naphthoquinone. No untoward reactions occurred and its action was prompt and effective. There were three cases in which the results were not satisfactory. In all of these cases there was some form of cirrhosis of the liver with marked impairment of hepatic function. Ansbacher and Fernholz (7) have shown that this compound was practically as active as Vitamin K. Rhoads and Fliegelman (8) have reported the use of this compound orally in ten cases. Andrus and Lord (9), and Macfie, Bach-

the gall bladder with hepatitis but without obstruction of the common bile duct, a delayed prothrombin clotting time developed several days post-operatively but was readily controlled. In four of the cases of intestinal disease with delayed prothrombin clotting time but without bleeding, similar good results were obtained. Three failures encountered were in the group of cases of cirrhosis. In one other case there was evidence of bleeding and this was satisfactorily controlled. Fig. 2 represents one of the cases of failure in which repeated injections of Vitamin K<sub>2</sub> and 2-methyl-1,4-naphthoquinone were given. It does show, however, that the prothrombin clotting time could be kept within reasonable levels, avoiding any hemorrhagic manifestations and without any toxic manifestations with dosage of this degree. The course of this patient's illness ended fatally. In the remainder of cases the treatment was prophylactic and no manifestations of

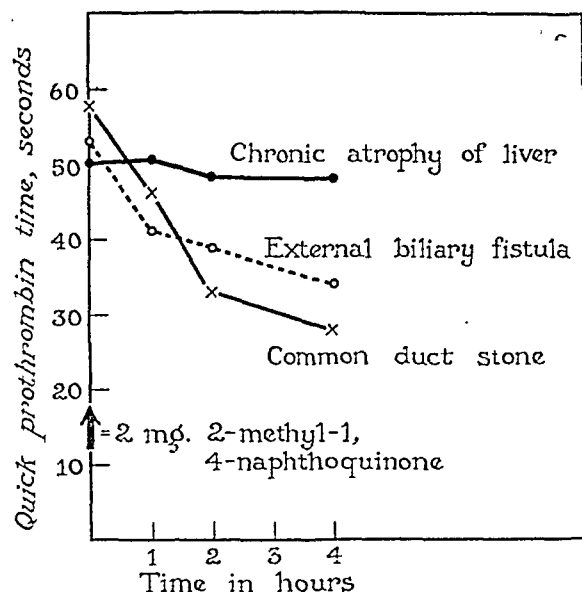


Fig. 3. Rapidity of action of 2-methyl-1,4-naphthoquinone on delayed prothrombin clotting time.

bleeding were encountered at any time during the period of illness.

#### RATE OF ACTION OF VITAMIN K AND SYNTHETIC COMPOUNDS

In the earlier work in regard to Vitamin K, the products available could be administered only orally. The rate of absorption from the intestinal tract was probably a variable factor. However, it was evident that a marked decline in a delayed prothrombin clotting time occurred within twenty-four hours. With the availability of soluble compounds administration could be carried out by the intravenous route assuring an instant availability of the antihemorrhagic compound to the liver. In all instances in which the compounds were effective the delayed prothrombin clotting time had returned practically to normal within twenty-four hours. In a few instances we have made determinations of the prothrombin clotting time at more frequent intervals. Fig. 3 represents the favorable response in two cases following the administration of 2 mg. of 2-methyl-1,4-naphthoquinone. Incidentally, the

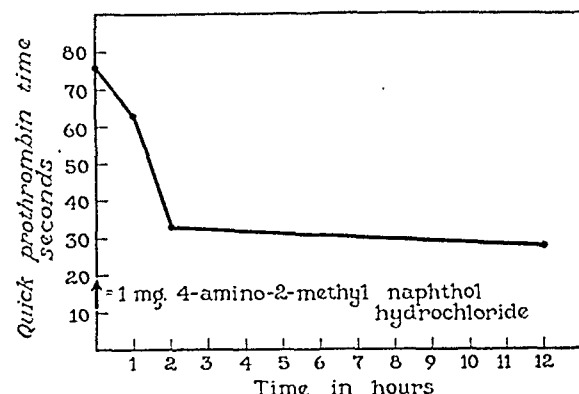


Fig. 4. Rapidity of action of 4-amino-2-methyl naphthol hydrochloride on delayed prothrombin clotting time.

lack of response in another case of chronic atrophy of the liver is also shown. Fig. 4 represents the rapid response within a period of two hours to 1 mg. of 4-amino-2-methyl naphthol hydrochloride.

Another very interesting observation occurred at the operating table. A patient with jaundice probably due to a stricture of the common bile duct and with considerable hepatic damage was undergoing an exploratory laparotomy. In spite of preoperative administration of antihemorrhagic compounds, oozing of blood was occurring freely from the edges of the operative wound. An intravenous injection of 2 mg. of Vitamin K<sub>2</sub> was given. Almost at once the oozing decreased and in a few minutes the wound was dry. Such observations are important in studying the method of action of Vitamin K. This rapidity of action is suggestive of possible enzymatic activity.

#### COMPARISON OF SYNTHETIC COMPOUNDS WITH ONE ANOTHER

We have had an opportunity to use in clinical cases four synthetic compounds that have Vitamin K activity. Table II is a comparative representation of our

TABLE II

COMPARISON OF NAPHTHOQUINONES FROM THE THERAPEUTIC STANDPOINT

	PHTHIOL	"NAPHTH-AL-DEHYDE"*	2-METHYL-1,4-NAPHTHO-QUINONE	VITAMIN K <sub>2</sub>
PATIENTS TREATED - 10		10	20†	45
ADMINIS-TRATION	ORAL	1 CASE	NONE	8 CASES
	INTRA-VEINUS	9 CASES	10 CASES	5 CASES
DOSAGE	50 MG. (25 TO 50 MG.)	10 TO 25 MG.	1 TO 2 MG.	1 TO 2 MG.
REACTION	0	0	0	0
FAILURES	0	2	3	3
REMARKS	SOME DIFFICULTY IN PREPARATION FOR INTRA-VEINUS USE	SOME DIFFICULTY IN PREPARATION FOR INTRA-VEINUS USE	USED INTRA-VEINUSLY AS A SOLUBLE SODIUM SULFONATE ADDITION COMPOUND	CAN ALSO BE GIVEN ORALLY OR INTRA-VEINUSLY

\*1,4-DIHYDROXY-2-METHYL-3-NAPHTHALDEHYDE.

†7 CASES RECEIVED BOTH ORAL AND INTRA-VEINUS ADMINISTRATION.

experience with them. All of these agents are relatively easily administered by the intravenous route although with the first two there was some difficulty in preparation and perhaps, as a result, they lost some of their antihemorrhagic properties. The preparation, 2-methyl-1,4-naphthoquinone, has been supplied in the form of tablets and in ampules and Vitamin K<sub>2</sub> has been supplied in ampules. These ampules may be given to the patient directly or their content may be added to solutions of glucose that are being administered. Results with all compounds have been eminently satisfactory. There has been a drop in the delayed prothrombin time nearly to normal in twenty-four hours and bleeding has been controlled. In cases in which the compounds have been given prophylactically, surgical procedures have been withstood without evidence of bleeding. The only failures have occurred in some cases of cirrhosis in which there has been severe hepatic damage and insufficiency. No local or systemic reactions have been encountered with the use of any of these compounds and there has been no sign of toxicity. As much as 175 mg. of pththiol was given

over a period of nine days and 45 mg. of naphthaldehyde was given over nine days. As much as 39 mg. of 2-methyl-1,4-naphthoquinone was given over nine days and Vitamin K<sub>2</sub> was given in doses of 1 to 2 mg. daily over a period of two weeks without any untoward reactions. Koller (11) has reported nausea and vomiting when 3 mg. of 2-methyl-1,4-naphthoquinone per kilogram of body weight was administered. Ruigh (12) also stated that doses ten thousand times the therapeutic dose may produce hemolytic anemia in animals. Molitor and Robinson (13) have also reported on the toxic effects of phthiocol, 2-methyl-1,4-naphthoquinone and Vitamin K<sub>1</sub>. However, the amounts of the compounds used in these experiments were much higher than any therapeutic doses utilized.

All of these compounds seem satisfactory from the standpoint of clinical efficiency in controlling hypoprothrombinemia. Factors such as ease of administration and cost probably will determine the preparation that will become routinely used.

### FAILURES

Both clinicians and investigators concerned with studies on animals have noted that serious degrees of prothrombin deficiency develop in the presence of advanced hepatic injury, and that neither the administration of concentrates of Vitamin K orally or parenterally, nor the use of the more potent compounds of naphthoquinone, will correct the condition completely. Studies on animals after partial or total hepatectomy confirm the earlier impression that the liver is the principal site of formation of prothrombin and that when a sufficient degree of hepatic injury is present no appreciable formation of prothrombin occurs, even when the supply of the antihemorrhagic vitamin is ample. As clinical experience has increased, more of these cases have been encountered. In two cases of cirrhosis a favorable response to 1,4-dihydroxy-2-methyl-3-naphthaldehyde failed to occur, in three cases a favorable response to 2-methyl-1,4-naphthoquinone failed to occur and in three cases a failure to respond to Vitamin K<sub>2</sub> occurred. With good reasons, clinicians have concluded that a prolonged prothrombin clotting time which does not respond to adequate therapy with Vitamin K is indicative of irreversible hepatic damage and a poor prognosis.

### CONCLUSIONS

1. Several factors of interest to gastro-enterologists are important in the development of hypoprothrombinemia. These include inadequate intake of food that contains Vitamin K, impairment of absorption owing to lack of bile in the intestine and owing to a deficient intestinal absorptive surface, and hepatic injury. Starvation, impaired appetite, vomiting (functional or organic in origin), diarrhea, discharge from intestinal fistulas, continued aspiration of gastric or intestinal content, diseases of the intestinal mucosa, short-circuiting of the intestine, biliary obstruction, external biliary fistula, disease of the liver and operative procedures and complications are factors that may influence the concentration of prothrombin in the plasma.

2. The isolation of Vitamin K, demonstration of its quinoid nature and recognition of the antihemorrhagic properties of a number of naphthoquinones have given us a number of synthetic compounds for clinical trial. We have used four such compounds

intravenously with excellent results. The intravenous administration possible with these compounds permits precise dosage, circumvents the variable factor of absorption and assures instant availability of potent antihemorrhagic substances. No local or systemic reactions have occurred and there has been no evidence of toxicity.

3. Evidence is presented to show that the rate of action of these compounds is very rapid. This rapidity of action is suggestive of possible enzymatic activity.

4. Failures with all these compounds were confined to cases of advanced disease of the liver, chiefly cirrhosis. Failures encountered in the earlier use of Vitamin K have been largely eliminated by prescribing adequate dosage in prophylactic and curative treatment, constant care in suspecting the possibility of hypoprothrombinemia and the use of intravenous preparations.

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### DISCUSSION

DR. JOHN G. MATEER (Detroit, Mich.): Dr. Weir's paper is very timely. There are five possible causes for a drop in the blood prothrombin and the development of a hemorrhagic tendency: First, the absence of bile salts in the intestinal tract, due to obstructive jaundice, which is generally appreciated by the medical profession; second, marked liver damage which Dr. Weir talked about, today, which interferes with the synthesis of absorbed Vitamin K into blood prothrombin; in the third place, grossly deficient absorption of Vitamin K from the intestinal tract as in sprue; in the fourth place, a gross deficiency of Vitamin K in the diet intake; and, in the fifth place, marked and repeated hemorrhage, which may aggravate the effect of any one of the above four primary causes.

I want to show you just one case that illustrates how hemorrhage itself may at least aid in maintaining a vicious circle of haemorrhage after the original drop in the blood prothrombin and the hemorrhagic tendency have been initiated by one of the four primary causes, viz, in this case, a gross deficiency of Vitamin K in the diet intake.

(Slide) This is a boy whom we saw over a year ago, one of the "type" cases we talked about at the A. M. A.

meeting a year ago, a boy fifteen years of age, who had had a very marked aversion of green vegetables, so much so that he developed neurotic vomiting whenever this type of food was suggested.

We saw him two weeks after the onset of his illness, which had consisted of gross hemorrhage from the intestinal tract which persisted day after day over a two-week period. During this two weeks of bleeding he had had daily transfusions of 250 to 300 cc. of blood; but, in spite of the small, daily intake of prothrombin in the repeated transfusions, the persistent loss of blood and the resulting loss of prothrombin from day to day, plus the fact that he still refused to eat any green vegetables, evidently resulted in the persistence of bleeding.

When we first saw this patient, in spite of his recent, daily blood transfusions, the blood prothrombin percentage was only 10%. (Dr. Weir referred to the prothrombin time in his paper, whereas we have converted the prothrombin time into the prothrombin percentage of normal,

using Quick's method). The hemoglobin of this patient, after all these transfusions, was still only 25 per cent.

When Vitamin K therapy was administered, the prothrombin rose promptly to a level of 60% in 48 hours; and the hemoglobin also rapidly rose to 60 per cent in a few days, following the prompt cessation of haemorrhage and further transfusions.

Nine months later this boy returned to the hospital with a recurrence of bleeding, again due to a low blood prothrombin. Since he had refused to add green vegetables to his diet, he is being protected now against further hemorrhage by taking each day a capsule containing synthetic Vitamin K.

In conclusion, we have used synthetic Vitamin K in a number of cases intravenously; and our experience has been similar to that of Dr. Weir. We have obtained no unfavorable reactions, and we have been impressed with the extremely rapid rise of the blood prothrombin following the intravenous method of administration.

## The Blood in Cases of Hematemesis and Melena with Reference to Factors Influencing Hemorrhage<sup>‡</sup>

By

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AN appreciable proportion of patients with hemorrhage from the upper gastro-enteric tract leave the hospital, after diagnostic procedures including X-ray and gastroscopic examinations, with the cause of bleeding undetermined (1). In some instances such causes as ulcer, varix, gastritis, or neoplasm may be demonstrated later, but often a source of hemorrhage is never discovered. Isolated observations have appeared in the literature correlating with hematemesis, one or another of the factors associated with bleeding tendencies. Portnoy and Wilkinson (2), Archer and Graham (3), and others (4, 5, 6, 7) have focused particular attention on the low plasma Vitamin C level in patients with ulcer, particularly those with hematemesis. Though these authors attributed the C deficiency to restricted ulcer diets, the known relationship of scorbutic states to hemorrhage has been emphasized.

It seemed desirable to make a systematic study of factors influencing bleeding in general, in patients with hematemesis and melena. In forty-four such patients admitted to the Cincinnati General Hospital, plasma ascorbic acid levels were determined and compared with those of normal individuals and other hospital groups. In addition the Duke and Ivy bleed-

ing times, serum phosphorus and calcium,† clotting time (method of Lee and White), prothrombin time, and blood fibrinogen were determined. In order to rule out blood dyscrasias, the formed elements of the blood and bone marrow were examined. Capillary resistance was determined by both positive and negative pressure methods.

### VITAMIN C

In an excellent paper, Portnoy and Wilkinson (2) reported cevitic acid levels in normal individuals, infirmary ward patients and in patients with peptic ulcer both with and without hemorrhage. They checked their findings by an intradermal 2-6 dichlorophenolindophenol test, by estimation of the daily urinary excretion of ascorbic acid and by various saturation tests. The plasma levels in their normals ranged from 0.6 to 1.85 mg. per cent, in keeping with the results of other observers. The concentrations in their general infirmary group were above 0.80, in comparison to ulcer patients whose levels varied from 0.14 to 0.59 mg. per cent with a mean of 0.42 for ulcer alone and 0.34 for ulcer and hemorrhage.

We have studied five groups of individuals seen in the Cincinnati General Hospital between July 5, 1939 and May 1, 1940.

Group I comprised twenty doctors, nurses and medical students on liberal diets with an adequate Vitamin C intake.

Group II consisted of twenty patients without acute infectious disease selected at random from the Out-Patient Dispensary of the Cincinnati General Hospital.

Group III was made up of thirty patients representing a similar cross-section of the hospital wards.

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†The serum phosphorus and calcium determinations were made in the laboratory of the Pediatrics Research Foundation, through the courtesy of Dr. George Guest.

‡This work was aided by grants from Parke-Davis & Company and the Kroger Food Foundation.

The Vitamin C used in this study was kindly supplied by Hoffman-LaRoche, Inc.

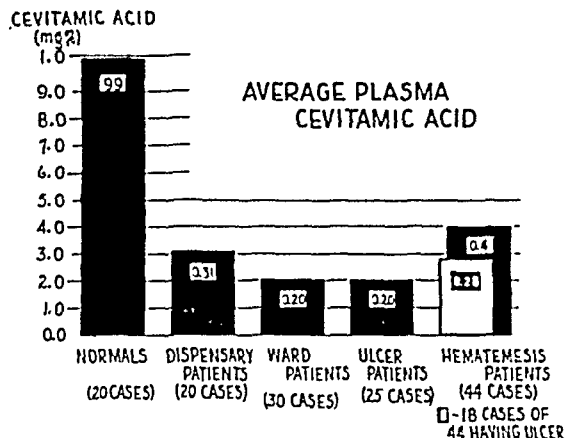


Chart 1

Group IV comprised twenty-five patients with peptic ulcer attending the Gastric Clinic of the hospital.

Group V included forty-four patients with hematemesis of varying degree of severity as they appeared on the medical wards of the hospital. Of these only seven represented gastric carcinoma or hepatic cirrhosis with varices. Of the remaining thirty-seven, eighteen had peptic ulcer and in nineteen the cause of bleeding was undetermined. They were studied as follows:

(a) Admission plasma cevitic acid levels were estimated for comparison with Groups I to IV.\*

(b) On twelve patients, Vitamin C saturation tests were performed as soon after admission as permissible and again upon discharge. All patients were on a Meulengracht diet during their hospital stay.

(c) An attempt was made to correlate plasma Vitamin C levels with the presence or absence of reduced capillary resistance.

Our normals averaged 0.99 mg. per 100 cc. of blood. The highest was 1.47. Only one was slightly below 0.6 mg. per cent. The highest figure for dispensary patients was 1.48 and the lowest 0.05; the average

TABLE I

Plasma cevitic acid levels in patients with hematemesis and melena

Mg. per 100 cc	No. of Cases
0.01-0.19	15
0.20-0.39	13
0.40-0.59	5
0.60 and above	11
Total	44

0.31, and among the ward patients the highest was 0.74, the lowest 0.03 and the average 0.20 mg. per cent. The highest plasma level in ulcer patients was 0.69 mg. per cent, the lowest 0.08, with a 0.20 average. As will be observed from Chart 1, there is no appreciable difference between general dispensary and ward patients, and ulcer patients with and without hematemesis; all groups being considerably under the usually accepted normal range.

\*Cevitic acid levels were estimated by the titration method of Farmer and Abt (8).

In our hematemesis group the results differed from those of Portnoy and Wilkinson. It is evident that these patients had levels below normal but they averaged 0.4 mg. per cent. If hematemesis due to ulcer be considered separately, the mean is 0.28 mg. per 100 cc. of blood, still higher than for ulcer without hemorrhage. More significant is the fact that eleven of the forty-four patients who bled had a normal Vitamin C (Table I). Further, seven of these eleven were patients in whom the cause of the bleeding was not determined (Table II). Thus the plasma cevitic acid level was adequate in thirty-six per cent of the

TABLE II

Etiology of hematemesis and melena in eleven patients with normal plasma cevitic acid

Etiology	Cases
Hepatic cirrhosis	1
Gastric carcinoma	2
Peptic ulcer	1
Undetermined	7

group in which we were most anxious to discover an etiological basis for hemorrhage.

### VITAMIN C SATURATION TEST

Twelve patients received the Vitamin C saturation test as described by Goldsmith and Ellinger (9) on admission and again upon discharge. These tests served as a check on the validity of a single estimation. Further, it seemed desirable to note any change in a patient's status after treatment with our modified Meulengracht diet (10) which contains approximately 30 mg. cevitic acid for the first two days and 50-70 mg. thereafter. In this test the gap between the urinary excretions of normal and deficiency states is large, eliminating confusion which might have arisen because of minor plasma level changes of questionable significance. It will be noted in Table III that those whose fasting plasma levels

TABLE III

Repeated cevitic acid saturation tests in twelve patients with hematemesis and melena with average hospital stay of twenty-three days

Case	On Admission		On Discharge	
	Fasting Plasma C Mg. %	6 Hour Urine Output-Mg.	Fasting Plasma C Mg. %	6 Hour Urine Output-Mg.
P. N.	1.2	164.8	1.0	156.4
F. R.	1.3	66.0	.96	169.5
P. S.	1.26	144.7	.97	107.3
F. W.	.81	302.0	.31	45.4
H. D.	.29	2.6	.29	5.4
O. D.	.15	9.1	.29	2.9
H. D.	.12	2.7	.30	3.2
C. M.	.07	4.2	.33	8.9
C. P.	.14	1.6	.16	6.3
J. S.	.17	4.5	.12	3.6
J. W.	.25	4.3	.25	13.1
C. W.	.14	3.3	.18	3.8



were normal excreted an appreciable part of the 600 mg. taken by mouth. Those whose C saturation was low excreted very little. No change in the state of saturation of any of these patients from the time of admission to the time of discharge was indicated by these tests. It is apparent that the daily intake provided by the Meulengracht diet, bearing in mind the additional cevitamic acid used in the admission test,

CHART II

*Relation of capillary fragility to plasma cevitamic acid levels in forty-four patients with hematemesis and melena*

Petechiae (+)	1	8
Petechiae (—)	10	25
	Normal Plasma C	Low Plasma C

is a maintenance dose. It neither reduced the state of saturation in normals nor improved the situation for those deficient in the vitamin.

#### VITAMIN C LEVELS AND CAPILLARY RESISTANCE

Were ascorbic acid deficiency concerned with hematemesis it should manifest itself by capillary fragility. An attempt was therefore made to establish the state of capillary resistance by two methods: (1) positive pressure of 100 mm. mercury on the arm for fifteen minutes, noting the presence or absence of petechiae

TABLE IV

*Plasma cevitamic acid in patients manifesting petechiae at time of hemorrhage and at varying intervals after hemorrhage*

Diagnosis	Plasma C (on admission) Mg. %	Pet.	Later Exam.	Plasma C Mg. %	Pet.
Undet.	0.25	+	7 months	0.26	+
Undet.	0.18	+	5 "	0.13	+
Undet.	0.10	+	1 "	0.13	+
Gast. ulcer	0.24	+	2 "	0.16	+
Duod. ulcer	0.49	+	7 "	0.26	+
Duod. ulcer	0.01	+	1 "	0.24	+
Hepatic cirrhosis	0.80	+	6 "	0.76	+
Hepatic cirrhosis	0.23	+	Died		
Gast. ulcer	0.35	+	Died		

in the antecubital area, (2) known negative pressure applied for one minute over 1 square cm. of antecubital skin by means of a glass cup. (The apparatus has been described by Elliot (11)). Two or more petechiae elicited in one minute by a negative pressure of less than 250 mm. of mercury constituted a positive test and conformed to a like manifestation by the positive pressure method. Normals required a negative pressure

of 300 to 400 mm. or more before rupture of capillaries occurred.

Nine patients manifested increased capillary fragility (Chart 2). In only one was the cevitamic acid level normal. All others had low plasma C levels but twenty-five showed no petechiae despite low C levels. Since our study was one of observation, no attempt was made to alter the vitamin status of these patients. We have assumed with Bourne (12), that the C level could be taken as indicative of the Vitamin P level since they occur together in natural foods. Our failure to correlate plasma C content and capillary fragility corroborates the findings of Farmer and Abt (13) rather than of Bourne and Rivers and Carlson (4). Finally, all those who manifested capillary fragility at the time of hematemesis again showed petechiae at a later date where the circumstances surrounding their hemorrhage could be considered to no longer exist (Table IV).

#### THE DUKE AND IVY BLEEDING TIMES

The Duke (14) bleeding time, estimated by noting the duration of bleeding following a small puncture wound, was normal in all cases. The results of the Ivy bleeding time were of interest but their interpretation difficult. Ivy (15) and his co-workers found that in certain hemorrhagic conditions, patients whose Duke bleeding time was normal evidenced prolonged bleed-

TABLE V

*The Ivy bleeding time in forty-three patients with hematemesis and melena*

Ivy Bleeding Time	Cases
2' to 3' .....	9
3'10" to 4' .....	21
Over 4' .....	13

ing if a positive pressure of 40 mm. of mercury were applied above the point of puncture. The test is not specific but is thought to reveal some fault in clotting factors or capillary contractility. Four minutes is considered the outer limit of normal by Ivy. Of the forty-three patients tested, thirteen bled for more than four minutes (Table V). Only one of our normals had an Ivy bleeding time of over four minutes. He also gave evidence of increased capillary fragility. Because of this, we attempted a correlation of the Ivy time with petechiae and the plasma Vitamin C levels but none was found. In those available for later examination, the Ivy bleeding time returned to normal in all but one patient.

#### SERUM PHOSPHORUS AND CALCIUM

The serum phosphorus was normal in seven patients with hematemesis in whom it was studied. The serum calcium was estimated in twelve cases. In six of these the levels were below the normal range of 9.0 to 11.0 mg. per 100 cc. of blood. Two others were at the lowest arbitrary figure of normal (9.0 mg. per cent). In the few who were re-examined later, the serum calcium had returned to normal (Table VI). There was no apparent relationship between serum calcium levels and any other of the factors studied. It was certainly not concerned with clotting time which was markedly

reduced in these cases. The significance of this finding remains obscure.

### CLOTTING TIME, PROTHROMBIN TIME AND BLOOD FIBRINOGEN

The clotting time of the blood of forty-two patients with hematemesis was estimated by a modification of the method of Lee and White. With this method, our normals ranged from twelve to sixteen and a half minutes. For patients with hemorrhage, the shortest

TABLE VI

*Serum calcium in twelve patients with hematemesis or melena*

Diagnosis	Serum Calcium On Admission	Serum Calcium 6-7 Mos. Later
Undetermined	7.8	
Duod. ulcer	8.8	
Gast. ulcer	9.6	
Duod. ulcer	8.2	10.3
Gast. erosion	8.6	
Undetermined	9.0	9.2
Duod. ulcer	9.0	10.1
Undetermined	8.6	10.6
Hepatic cirrhosis	10.5	10.3
Undetermined	10.4	
Undetermined	9.8	
Gast. cn.	8.8	

time was six minutes, the longest twelve and a half minutes, the average nine. This was in keeping with the known decrease in clotting time following hemorrhage in general. Those whose clotting time was again determined at a late date were found to be within normal limits. Clot retraction was normal in all instances.

The method of Quick (16) was used in estimating the prothrombin time.\* In all but one of the patients with hematemesis, the time was within the normal limits. The results are shown in (Table VII). The

TABLE VII

*Prothrombin time in forty-three patients with hematemesis and melena (method of Quick)*

Clotting Time (seconds)	Cases
Below 16	36
16 to 20	6
22	1

only patient whose prothrombin time was longer than twenty seconds and thus in the range consistent with a hemorrhagic state had severe hepatitis, proved by autopsy.

In discussing La Due's (17) work on hemorrhage associated with peptic ulcer in 1939, Frank mentioned that in every patient with bleeding ulcer in his series,

\*Thromboplastin used was furnished through the kindness of the Kroger Food Foundation.

the prothrombin content of the blood was less than 70 per cent normal. The prothrombin content of the blood in twelve of our cases was estimated by the quantitative titration method introduced by Smith and his associates (18). Results are expressed in units, normals ranging from 280 to 320. A specimen of normal blood is examined simultaneously and the unknown expressed in percentage of normal. Excluding W. R., the patient with hepatitis mentioned above, only three patients were below 70 per cent of normal and none approached the critical level for hemorrhage (Table VIII).

Blood fibrinogen was determined in twenty-four patients by the method of Greenberg (19). The normal range is 200 to 400 mg. per 100 cc. of blood. In none of our patients with hematemesis was it below 200 mg. per cent. The average was 353 mg. per cent.

### BLOOD PLATELETS AND BONE MARROW

The platelets were well above the critical level for bleeding, ranging from 108,000 to 800,000 cubic mm.; averaging about 300,000 per cubic mm.

In fourteen patients studied, bone marrow, biopsied

TABLE VIII

*Smith plasma prothrombin content (units) in patients with hematemesis or melena (10 cases)*

Case	Units*	% of Normal**
G. L.	293	97
G. M.	175	58
W. F.	195	69
R. B.	204	72
W. R.	79	24
H. M.	182	59
L. W.	277	91
J. S.	264	87
W. R.	290	91

\*Normal 280-320.

\*\*Percentage relation of prothrombin in the blood of a hematemesis patient to that of a normal patient tested simultaneously.

by sternal puncture, showed no change other than increase, in some instances, in the erythrocyte series which was interpreted as a manifestation of blood regeneration. Megakaryocytes were present in normal number. There was nothing in the cytological studies to suggest the presence of blood dyscrasia.

### SUMMARY

Forty-four patients with hematemesis and melena were studied on the Cincinnati General Hospital wards to determine whether any single factor or combination of factors associated with hemorrhage in general bore any relation to the episode.

Plasma Vitamin C levels were determined upon admission and compared with levels of normal individuals, groups representing a cross section of the Cincinnati General Hospital wards and dispensary and a group of ambulatory peptic ulcer patients who were not bleeding. We found, as have others, that peptic ulcer patients on restricted diets have lower average plasma C levels than patients at large. In contrast to

the findings of others, however, our hematemesis cases had higher average levels than those of patients with ulcer alone. That over 20 per cent of our patients bled, with the C level within the normal range casts doubt on the etiological significance of the Vitamin C level.

Vitamin C saturation tests were performed on twelve patients on admission and discharge, and were found to be low in 8 instances. No change in the state of saturation was noted following an average stay of 23 days on a modified Meulengracht diet.

The state of capillary resistance was established in these patients with hematemesis by both positive and negative pressure methods. No adequate correlation between plasma cevitamic acid levels and the appearance of petechiae could be obtained, corroborating the reports of Farmer and Abt. Further, patients who showed petechiae on admission again manifested lowered capillary resistance months after the hemorrhage.

Though the Duke bleeding time was normal, the Ivy bleeding time was prolonged in thirteen of the forty-three patients studied. No correlation existed between this finding and other factors associated with bleeding. In those patients studied at a later date, the Ivy bleeding time had returned to normal in all but one case.

The serum phosphorus was normal in the seven patients studied. The serum calcium, however, was slightly below normal in half of the twelve patients in whom it was determined, subsequently returning to normal in all those available for later examination. Again no correlation between this and other factors concerned with hemorrhage could be established.

The clotting time (method of Lee and White) was shorter than normal as would be expected following hemorrhage and returned to within the normal range in those re-examined at a later date. The prothrombin time (method of Quick) was below the critical level for hemorrhage in all but one patient who had a severe hepatitis, proved at autopsy. The quantitative esti-

mation of prothrombin (method of Smith et al) in twelve patients revealed only four patients whose prothrombin units were less than 70 per cent of normal, and only one (the patient with hepatitis mentioned above) whose prothrombin content was below the critical level for bleeding. Normal blood fibrinogen was found in all cases.

A study of the blood platelets in all forty-four patients and examination of bone marrow biopsies in fourteen, gave no evidence of blood dyscrasia.

### CONCLUSIONS

(1) The plasma Vitamin C content may be normal in hematemesis or melena due to peptic ulcer or undetermined cause.

(2) The average plasma C level of patients with bleeding peptic ulcer, though reduced, may be higher than that of patients with peptic ulcer without hemorrhage.

(3) The low Vitamin C plasma levels seen in patients with bleeding peptic ulcer or hematemesis of undetermined cause usually persists after cessation of hemorrhage.

(4) Prolongation of the Ivy bleeding time or reduction of serum calcium may occur in hematemesis due to peptic ulcer or undetermined cause. The significance of these changes is not clear.

(5) Significant prolongation of prothrombin time or reduction of prothrombin content of the blood does not occur in patients with hematemesis or melena due to peptic ulcer or undetermined cause.

(6) There was no prolongation of the clotting time nor Duke bleeding time and there was no reduction in the quantity of blood fibrinogen in patients with hematemesis due to peptic ulcer or undetermined cause.

(7) The bone marrow shows only evidence of blood regeneration and there is no significant reduction in the number of platelets in patients with hematemesis or melena.

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## The Present Status of Gastrectomy\*

By

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SINCE Billroth performed the first successful resection of the pylorus for carcinoma in 1881 the indications for gastrectomy and the extent of the resections made have been amplified with increasing experience. The routine employment of the operation today offers a marked contrast to the statement of Langenbeck, who in commenting on Billroth's efforts, stated that he looked on the attempt as "only a quicker way of taking out of the world a patient whom it was impossible to save." The literature has become voluminous, particularly as it relates to the application of gastrectomy to the cure of ulcer and while still highly controversial certain trends are definitely noticeable as a result of the recorded experience of surgeons throughout the world. The technique of gastrectomy will not be considered and the types of resection will not be discussed other than in elucidation of the principles involved. A review of the present status of gastrectomy will of necessity involve a limited discussion of the lesions for the cure or amelioration of which the operation is undertaken with the greatest attention focussed on the indications and results. The objectives, to the attainment of which increasing attention must be given, are, safety of operation, good function and protection against recurrence of the disease for which the operation is done. The preoperative care is of the utmost importance in determining the indications for surgical procedure, the most opportune time for it and in making it possible to perform with relative safety difficult operations when the risk is necessarily great. Of equal importance is the care during convalescence, particularly in securing rest of the stomach and upper intestine and in maintaining a proper food, fluid and blood balance. These principles are recognized as applying to all resections and their universal application has done much in reducing the immediate mortality. The mortality from gastric resections has reached a point where such operations may be done without prohibitive risk, the paramount question now being their efficacy in curing lesions of the stomach and duodenum. These two factors, the risk of the operation and the possibilities of cure or amelioration, are the yardsticks by which gastric resections are to be measured. Since it is our intention to limit our discussion to underlying principles, the preoperative preparation, the anaesthetic agent employed, the technique of the operative procedure and the post-operative treatment are but mentioned with a statement of their importance in influencing the immediate mortality.

Gastrectomy in the treatment of carcinoma of the stomach is applied with one of two ends in view, palliation and cure. In the presence of demonstrable metastasis indicating utter hopelessness as far as cure is concerned the relief of disagreeable symptoms, par-

ticularly obstruction, afforded by partial gastrectomy fully justifies its employment in intelligently selected cases. Prolongation of life may be secured and death from metastatic lesions may be less painful and less distressing than that from starvation induced by gastric obstruction and retention in those patients in which the primary growth can be thoroughly removed. When the extent of the growth or its attachments prevent this desideratum, incomplete removal is worse than useless.

The three types of gastrectomy which find a place in the attempted cure of the disease are pylorectomy by the Billroth I, partial or subtotal gastrectomy by the Billroth II or one of its modifications, and total gastrectomy. Resectability depends on a number of factors, the important ones being accessibility, the extent of the growth, involvement of adjacent lymph nodes, distant metastases, and the age and condition of the patient. The optimal conditions for cure demand wide removal of the growth and the regional lymph nodes. The limitations of removal depend on two factors, one, the extent of the growth and the general physical condition of the patient, the other, the experience of the surgeon and his willingness to undertake radical resections with their increased mortality. While in the treatment of cancer operative mortality is of secondary importance, it should not be such as to prohibit patients from accepting the opportunity for relief which surgery offers. The use of the Billroth I operation for the removal of pyloric cancer, in which the pylorus and more or less of the adjoining segment of the stomach are resected with establishment of gastro-intestinal continuity by suturing the duodenum to the stomach, is open to two important objections, namely, the limited amount of stomach resected and the fact that if recurrence takes place at the site of anastomosis, the original obstruction is reproduced. These disadvantages are outweighed by its ease of execution in elderly patients of low resistance presenting small carcinomas in the antrum and who show sufficient mobility of the pylorus and duodenum to make the growth readily and quickly removed. Its applicability in the treatment of cancer is limited to this one group. Partial or subtotal gastrectomy by means of the Billroth II operation or one of its modifications which combine a wide resection of the stomach with closure of the duodenum and establishment of gastro-intestinal continuity by an anastomosis of the jejunum with the remaining portion of the stomach, offers the widest field of usefulness in the curative treatment of gastric carcinoma. It offers opportunity for the increasing tendency for more extensive resections for cancer here as elsewhere. Since in the light of our present knowledge the only prospect of cure lies in extirpation of the growth and since a perfected technique has largely eliminated the dangers of serious complications directly attributed to the

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operation itself, such as hemorrhage and defects in the line of suture, the problem of management becomes one of recognition at a time when such treatment can be carried out. The inherent difficulties in the early recognition of cancer of the stomach is graphically illustrated by the fact that, taking the country by and large, but 1 in 4 cancers of the stomach are amenable to resection at the time of their diagnosis as such. Herein lies the challenge to be met if improvement in results are to be attained in the treatment of the disease in the organ in which it shows its greatest incidence. The absence of early symptoms or, if present, their lack of impressiveness and of an appreciation of the necessity for adequate, competent study and examination are fully recognized by the members of this and other highly trained groups, but urgency of action on the part of the profession at large and of the intelligent members of the laity is yet to be accomplished.

The known tendency of cancer to spread along submucosal routes, neither visible nor palpable in its earlier progress, demands that the resection be a wide one: of equal importance is the removal of the regional lymphatics. While there is no reason for the adaptation of operations for carcinoma to influence gastric chemistry, it is interesting to note that the curability has been found to be higher in those showing achlorhydria than in those showing the presence of acid, the higher the value of the acid the less the prospect of cure.

The average mortality in experienced hands approximates 10 per cent and the ultimate result in the operable group compares favorably with that obtained in internal cancers situated elsewhere when the criteria of operability are fairly considered.

Total gastrectomy implies the removal of the stomach as a whole, including a portion of the duodenum and of the esophagus. The difficulty of its execution, its high mortality and the fact that life subsequent to it is relatively short combine to give it but a restricted place in the treatment of gastric cancer. The accepted indications for its employment are, a carcinoma involving practically all of the stomach without evidence of distant metastases: sufficient mobility of the stomach, pylorus and lower end of the esophagus to make the operation possible from a technical viewpoint: and the condition of the patient such that an operation of this magnitude may be undertaken with reasonable hope of recovery. The mortality in the reported cases has averaged 40 per cent with practically all the survivors dying within a five-year period. Many of the latter developed a marked secondary anemia, usually associated with metastases, although an instance of severe secondary anemia has been reported in which, at autopsy, no metastasis was found. While Mann and Graham have shown an absence of anemia in dogs four years after total gastrectomy, the question of the effect of the total absence of the gastric wall and its secretions on the physiologic activities of the body of the human offers a problem. Both clinical and laboratory experience have proved that the retention of a part of the stomach suffices to protect against a pernicious type of anemia which at first was feared would follow large gastric resections. It has also been shown that in both patients and animals the physiologic digestion of proteins, fats and carbohydrates, when properly

fed, is not seriously affected by the loss of pepsin and hydrochloric acid entailed by total gastrectomy. The work of Castle and Locke, demonstrating an "intrinsic gastric factor" having to do with erythropoiesis, has been confirmed by other investigators and would seem to indicate that a relationship exists between the stomach and the concentration of erythrocytes and hemoglobin in the circulating blood. These findings make tenable the hypothesis that total gastrectomy is of itself a contributing factor to the secondary anemia observed following its usage in the treatment of cancer.

In discussing the status of gastrectomy in the treatment of ulcer, probably a better perspective can be gained by a consideration of its present employment in the various phases of the disease. The surgical treatment of patients with peptic ulcer has shown a progressive change from a conservative to a radical attitude in the last two decades. The simpler procedures of gastrojejunostomy and plastic operations on the pylorus were at first hailed with enthusiasm and widely employed. With the lapse of sufficient time for the evaluation of ultimate results these operations were found to have definite disadvantages and have been largely replaced first by resection of the pylorus and later by subtotal resection of the stomach. While the conservative procedures still have their advocates, the field of their employment is becoming progressively more restricted. Duodenal ulcers on the posterior wall associated with bleeding, deeply penetrating lesions, multiple ulcers, gastric ulcers that do not decrease in size under treatment, those with an extensive gastritis and those with a high gastric acidity, all demand more than a palliative short circuiting operation for their relief. It is recognized that peptic ulcer is primarily a medical problem and that its mere presence cannot be considered an indication for the application of surgery. The indications for operation are now fairly well established and opinions crystallized as to the advisable time for carrying out surgical treatment. The same unanimity cannot be said to exist regarding the extent of the operation, but there is a definite trend to more and more radical resections. Whatever the cause of ulcer abundant and conclusive clinical experience has demonstrated its close relation to the presence of acid. The simpler conservative operations neither eradicate the accompanying duodenitis and gastritis nor sufficiently reduce the gastric acidity, the recognized factors of importance in relation to recurrence and both of which are amenable to resection. It is true that the primary mortality of the simpler conservative operations is lower than that of resection, but when the mortality of the secondary operations in patients showing recurrence following the primary employment of the simpler operations is considered, the combined mortality of the two groups is shown to approximate that of primary resection. This statement will not hold with reference to all clinics and surgeons, but it is a true reflection of the country at large. The three conditions sought by the proponents of gastrectomy in the treatment of ulcer are, 1—the elimination of the ulcer and ulcer-bearing area; 2—the restoration of physiologic activity; and 3—protection against recurrence.

Gastric Ulcer. The indication for the surgical treatment of gastric ulcer is relatively simple, namely, one

that does not heal under intelligently directed medical treatment. Persistence of ulcer in spite of appropriate medical treatment of necessity arouses a suspicion as to its innate character and the safety of the patient demands an answer. The safety of the patient equally demands an operation that will afford protection regardless of the microscopic structure of the ulcer, information that can be obtained only after its removal. Local excision alone, local excision or cautery destruction supplemented with gastro-enterostomy, gastro-enterostomy, sleeve resection and resection of the pylorus have all been tried and found wanting in that incomplete relief of symptoms and recurrence of ulceration have been so frequently noted. The consensus of opinion of the present time is that subtotal gastrectomy is the operation of choice for gastric ulcer, reserving the simpler operations for those patients whose condition is such that the risk does not justify the operation. Once a decision for resection is reached those with the greatest experience advocate carrying out a really radical removal of the stomach. While pylorectomies and antrumectomies have a mortality rate as high as partial resection, they have little advantage over gastro-enterostomy, since they fail to remove a sufficient amount of the stomach and consequently fail to decrease gastric acidity. The advocates of subtotal gastrectomy set three-fourths to four-fifths of the stomach as the amount to be resected, claiming that less extensive resections fail to produce anacidity or hypoacidity and that a recurrence of symptoms may follow the failure to obtain this result. In our opinion these arguments do not have the same force when applied to gastric ulcer as when applied to duodenal ulcer, since the recurrence of ulcer in the stomach, at the stoma and in the jejunum are observed far less frequently following resections for gastric ulcer than after operations for duodenal ulcer. The ever present possibility of carcinoma in gastric ulceration and the difficulty, in fact the impossibility of its identification in all cases at the operating table has led to the general acceptance of resection as the treatment of choice in gastric ulcer, granting its accessibility and its operability, when the general condition of the patient does not prohibit the employment of an operation of this extent.

**Duodenal Ulcer.** The real problem in the present status of gastrectomy comes in attempting to define its place in the treatment of duodenal ulcer. Assuming that surgery is employed only in cases of intractable chronicity, perforation, obstruction and hemorrhage, one runs counter to many diverse opinions as to the value of gastrectomy in the surgical management of these complications. All are agreed that the routine employment of gastro-enterostomy or of plastic operations on the pylorus in all cases is, in many instances, but asking for further trouble. The American profession was slow in accepting the hypothesis advanced by Finsterer in 1920 that where there is no acid there will be no ulcer. It cannot now be said to have unanimously adopted the surgical procedure having as its objective the production of anacidity, but the trend is definitely in this direction. Ulcers showing intractable chronicity and presenting no complicating features offer the real bone of contention, the advocates of conservative surgical measures claiming 90 per cent relief with a low operative mortality, while those favoring resection have been led to adopt the radical measure

by failure to obtain relief from symptoms and by noting recurrence in from 2 to 30 per cent of the patients upon whom they had performed conservative surgical procedures. The degree of hypersecretion and the increase in acid, are, in most instances, in inverse ratio to the patient's age; thus the control of ulceration in the young individual presents a difficult problem, the solution of which increasing experience indicates to be a sufficiently wide resection of the acid-bearing surface to produce anacidity or at least hypoacidity. A resection of less extent carries with it a greater operative risk than and has no compensating advantage over the simpler procedures. Studies of the acid values in patients subjected to partial gastrectomy have shown varying results, apparently depending on the extent of the resection, approximately 70 per cent obtaining a relative achlorhydria: in the group in which acidity was retained recurrences have been noted, while in the one in which anacidity obtained they have been absent. This observation has led to a certain standard, particularly in younger patients with high acid values, contemplating the removal of the pylorus, antrum, greater portion of the lesser curvature and at least three-fourths of the body of the stomach. A truly extensive operation, but for which justification is claimed by ultimate results. In patients suffering from ulcer stenosis at the pylorus, particularly in the upper age levels, the long duration of the disease results in atrophy of the gastric glands with a low acid content in the stomach. Establishment of drainage in such instances by means of gastro-enterostomy has afforded beneficent results, yet in the recent literature the suggestion is made that after the patient has been rehabilitated by the provision of drainage, the abdomen be reopened and resection carried out as a protective measure. In my opinion only when massive or repeated hemorrhage has been a feature in the history is such advice acceptable. In perforations sealed by adherence to adjacent structures resection is the operation of choice when the general condition of the patient and the local pathology permit of its execution without prohibitive risk. The indication in acute perforation is the saving of life: this is accomplished by stopping the leak. We have encountered rare instances, notably calloused ulcers on the lesser curvature immediately adjacent to the pylorus, in which satisfactory closure could not be accomplished by suture and in which we have resorted to primary resection with no untoward result. It is interesting to note that Professor S. S. Judin of Moscow, in *Surgery, Gynecology and Obstetrics*, January, 1937, in reviewing his experience with acute ulcer perforations at the Central Emergency Hospital in Moscow has come to the practice of resection as the operation of choice in the younger patients admitted to the hospital within six to eight hours after perforation. During 1933 and 1934, 80 per cent of the admissions for acute perforation conformed to these specifications, and 331 were subjected to resection, 293 by the Billroth I and 38 by a modified Billroth II: there were 26 deaths, a percentage of 7.8. During the same period conservative operations were done on 87 patients with acute perforations, including those in the higher age levels and those admitted late after perforation, with 28 deaths, a mortality of 32.2 per cent.

The problem of the bleeding ulcer is one upon

which there is as yet no unanimity of opinion. It has long been conceded that ulcers showing a tendency to bleed should be destroyed or removed, even when treated by conservative surgical measure. It is now conceded by all that ulcers with a history of serious and repeated hemorrhage should be treated by resection, with proponents for the Billroth I and a limited resection and proponents for the Billroth II and a wide resection. The best of the argument in my opinion lies with the latter group, since the objectives are, first, to get rid of the ulcer and, second, to afford protection against recurrence. In the presence of massive hemorrhage a choice of medical or surgical management must be made, and in the event of a selection of the latter, a choice between ligation of the bleeding artery in the bed of the ulcer, ligation of the duodenal arteries supplying the ulcer and partial resection. The mortality from hemorrhage in duodenal ulcer is an appreciable one, it being estimated on statistical reports at 3 per cent of the total number. However, if the mortality estimation be limited to the ulcers showing bleeding, the reported mortality varies from 5 to 16, with an average of 9.8 per cent. The death rate is much higher in patients of 50 or over than in younger ones, presumably due to the sclerosis of the vessels in older patients, making more difficult the establishment of thrombosis. The mortality is definitely less when the operation is carried out within 48 hours after the onset of the bleeding than when patients are carried along on transfusions and a medical regime until these have been demonstrated to be futile in controlling the bleeding. While subtotal resection is desirable, the radical procedure will have to be modified or abandoned with substitution of direct or indirect ligation as the condition of the patient warrants. In any event, operation on patients depleted by blood loss, even with multiple transfusions as adjuvants, carries a higher risk than when the operation is done during the quiescent, non-bleeding interval. Finsterer is a strong advocate of immediate

operation, pointing out that he had a surgical mortality of 4.3 per cent for a series of 46 cases in which patients were operated on within 48 hours of the onset of hemorrhage, and a mortality of 32.7 per cent for 55 cases in which the patients were operated on after 48 hours. Jejunal and gastrojejunal ulcers following gastro-enterostomy present the same indications for gastric resection as do the original ulcers and offer technical difficulties in its execution that entail a proportionately higher mortality.

While clinics and individual surgeons have reported impressive series of subtotal gastrectomies for ulcer with a mortality as low as 2 per cent, the death rate for the country at large will more nearly approximate 8 or 10 per cent, proving that it is a serious operation and one not to be undertaken too lightly. More and more surgeons, dissatisfied with the results of simpler measures, are turning to it and there can be no doubt but that in selected cases it gives excellent results. It is the operation that is followed by the lowest acid values and by the smallest number of recurrences and the one which gives the greatest relief. The fact that recurrences are noted following this procedure means that the gastric acid has not been adequately controlled or that the gastro-intestinal mucosa of the patient is peculiarly susceptible to ulceration: which again may be interpreted as meaning that the cause of ulcer remains obscure. In seeking a solution of the problems presented by ulcer, surgery has not been static. It has sought to adjust itself to the clinical variabilities of the disease and to changing viewpoints as to its cause, to the difficulties of instituting surgical treatment at the most favorable time, to new and revised methods of treatment and to shifting concepts of physiology, particularly as it applies to restoration of function following various operations. Conforming to these objectives and to our limited knowledge of the etiology, gastrectomy, in selected cases, offers today the best chance for cure.

## Gastrectomy, Partial, Subtotal and Total, the Radiographic Phase

By

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**W**HEN we were invited to discuss the roentgenographic aspects of gastrectomy, it seemed difficult to know just how to approach the subject. After considerable thought we decided to take up first the one unquestionable indication for gastrectomy, namely cancer.

Looking over the statistics of the Lenox Hill Hospital for the period of 1923-1934, we were impressed at once by the high mortality of cancer of the stomach. 201 of 255 cases of malignancy of the stomach were operated with a hospital mortality of 33%. 49 of these cases were resected with an immediate mortality of 42.8%. 89 had exploratory—no surgical procedure could be carried out. The remaining 63 had palliative

gastro-enterostomy. To date (1940) of those living after resection during that period, who could be followed, one lived one year, one lived two years, one seven years, one nine years, one was alive nine years, after then lost track of, and two were alive after ten years.

It is evident, from these figures, that when these cases reached the surgeon they were so far advanced as to be almost hopeless under any form of gastrectomy. With the hope of stimulating an earlier diagnosis we are presenting what we believe to be the most modern method of X-ray examination of the stomach. Before describing this technique we would suggest that the propaganda and publicity which has been carried on by so many societies and public officials to make the public cancer conscious, be continued and in-

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creased, so the laity consult their physicians early, namely when they have loss of appetite and loss of weight with slight indigestion, because then is the time when the roentgen examination can reveal what no other method has succeeded in doing, namely the early diagnosis of cancer of the stomach.

Having persuaded our patient to consult his doctor at an early date, we must now work on the medical consultant to make him also "cancer minded," so that he will, no matter how vague the clinical symptoms are, immediately think of having an X-ray examination made.

It is known that at this early stage of malignancy, the clinical symptoms are slight, indeed almost nil. But such cases, however, frequently show distinct positive roentgen signs of the lesion. This applies especially to cancer of the body of the stomach with no obstruction at the inlet or outlet.

The X-ray examination must be made by a competent roentgenologist who will not jump at conclusions but will give his opinion by carefully weighing his findings and using the most modern methods in ascertaining the facts. What, then, is this modern method so frequently spoken of, which is to be used in all cases of suspected cancer of the stomach? The following is a brief outline of the procedure.

The patient presents himself at an early hour with an empty stomach, a preliminary film is made to exclude any abdominal lesion visible without the means of an opaque meal. Four ounces of barium, with a suitable vehicle agreeably flavored, is then fed to the patient in the erect position. Under fluoroscopic control snap films, made possible by a switch-over arrangement from fluoroscopy to radiography, are made during the examination. The fluoroscopic screen must have a Bucky grid attached to provide a better image. Next the patient is placed in the prone position with a Chaul bag arranged to give a variety of pressures to the stomach region and a series of polygrams consisting of four images on one 10 x 12 film of the mucosal pattern are made under fluoroscopic control. This procedure may be repeated at the six hour visit. Then follows a series of films made in the erect, supine, prone and oblique positions, in sufficient number to satisfy the examiner. The old idea that you have to have twenty or thirty films to make a diagnosis is obsolete. With the coming of the spot film and pressure technique fewer films are required.

At this point, one may remark about the rule advocated by many roentgenologists, when using the old technique, namely, that one normal film in a series is sufficient to exclude the diagnosis of a lesion, even if the majority of the other roentgenograms show defects, has been proven erroneous and misleading. In our experience many cases which appeared normal under ordinary technique showed defects indicating pathology when submitted to a special device.

### THE DEFECT; ITS LOCATION

Let us consider for a moment the deformity which is recognized as cancer. First we note its location. Ulcers on the lesser curvature, below the angularis, especially when within one inch of the pylorus, must be looked upon as suspicious of cancer (2). Deformi-

ties on the greater curvature are in a very large percentage indicative of malignancy and lesions at the fundus have proven to be mostly cancerous.

### SIZE OF THE DEFECT

It has been said, for many years, that the size of the lesion indicates whether it is benign or malignant. We know now this is a fallacy and to depend upon it is often very misleading. While large lesions are probably positive, the smallest of ulcers may indeed be cancers.

### THE SHAPE OF THE DEFECT

In general, it is important in the recognition of cancer. The contour is, as a rule, irregular with sharply cut edges. It does not have the budding and contracting defect of ulcer and most cases show the "halo" or meniscus sign described by Carman. In cancer of the infiltrative type, there is a flattened area, especially on the lesser curvature, showing only a little stiffness and notching. The old teaching that a peristaltic wave will jump the area, is another sign difficult to recognize, especially in smaller lesions. Even when of considerable size, the shift to and fro with peristalsis renders the recognition of the jump confusing. The flat defect looks like an inlay in the stomach wall. It may become triangular in shape with the apex protruding beyond the stomach wall (3).

Beside the ulcerated and indurated type of cancer we have the type in which there is projection of the tumor tissue into the cavity of the stomach. It may or may not have an ulcerated surface. Tumors of this sort occur mostly on the greater curvature and give quite a characteristic filling defect. The occasional tumors of the fundus are generally malignant. Few of them are operable.

The decisive procedure where there is question as to the X-ray diagnosis, is to put the patient to bed and let him rest for a time. He may gain in strength and weight but when roentgen findings remain the same, or show increase of involvement, cancer is the answer.

There are, however, a few cases where the defect is actually filled with cancerous tissue so that the re-examination gave a false impression of disappearance of the lesion. It has been said that mucus will also cause disappearance of the shadow. Manipulation or lavage should displace the plug.

We have attempted to enumerate the advance made in the radiological diagnosis of early cancer of the stomach, believing that the roentgen findings are the most certain factor for the surgeon to consider in forming his decision about gastrectomy.

Finally, it must be admitted that even with all our skill and modern methods there are a certain percentage of cases in which it is almost impossible to recognize a malignant lesion. In such cases it is best to advise operation and to consider the process malignant until proven otherwise.

Of late years the use of the flexible gastroscope has become more and more in vogue. From our experience, except in the hands of an expert, it has been only valuable as confirming the X-ray findings.

The roentgenologic demonstration of complications



in gastric resection is concerned with early and late malfunction of the anastomosis. This may be due, in early cases, to edema of the stoma, adhesions or kinking. If the case is malignant we meet with recurrence. It has been said that once surgery has been resorted to "all bets are off" as far as X-ray interpretation is concerned. This would not apply if control films are obtained before the patient left the hospital following the resection.

In our experience marginal ulcer in resection is practically unknown in contra-distinction to their not infrequent occurrence in simple gastro-enterostomy.

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# The Effects of Gastrectomy in Animals\*

By

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**O**BSERVATIONS on gastrectomized animals show that the stomach cannot be considered as an essential organ in a strict sense. Observations on man and animals show that the stomach manifests the following functions: 1. *Reservoir function.* The reservoir function renders it possible to ingest a large meal in a short period of time. 2. *Triturating function.* The movements of the stomach function to decrease the size of the food particles and to mix the food with the gastric juice and to eject from time to time relatively small quantities of chyme into the intestine. 3. *Digestive function.* The hydrochloric acid-pepsin in gastric juice reduces protein to proteoses and peptones, which represents the first stages of protein digestion. Fats may be emulsified to some extent by the acid and the movements of the stomach. The ptyalin of saliva continues to digest cooked starches in the stomach until the enzyme is inactivated by the gastric acidity. 4. *Hematopoietic function.* The stomach secretes an "intrinsic factor," probably an enzyme, which acts on "extrinsic factors" in the food to produce a substance that has anti-pernicious anemia properties. This substance is sometimes referred to as the erythrocytic maturation factor, which after absorption is stored in and possibly worked over by the liver. Observations on animals and man indicate that the "intrinsic factor" or enzyme is also produced by the intestine. 5. *Bacteriostatic and bacteriocidal function.* By virtue of the acidity of gastric juice certain organisms are killed or inactivated in the stomach. 6. *Co-absorptive function.* By virtue of its digestive, reservoir and triturating functions, the stomach facilitates the absorption of calcium and iron in food.

The importance of these various functions is best determined by removal of the stomach. The stomach of numerous rats, pigs, dogs, puppies and monkeys have been totally removed in our laboratory since 1922, and the consequences of the loss of the various functions of the stomach have been studied or observed.

*Loss of the reservoir function.* The dog immediately ceases the bolting of food (1). After several months food may be ingested more rapidly, due in part to

some dilation of the upper intestine and other compensatory factors. The rat, pig and monkey also eat less at a time.

When a subtotal gastrectomy is performed on the dog, the gastric remnant undergoes much hypertrophy if he persists in bolting large meals (2). Along with the hypertrophy, gastric secretion returns and jejunal ulcer may occur. But jejunal ulcer never occurs after all the acid secreting mucosa is removed. When a radical subtotal gastrectomy is performed on the dog, so as to leave little more than cardiac mucosa, the capacity to secrete acid is markedly reduced (22, 23). The discrepancies cited in the literature, we believe, are due chiefly to variations in the extensiveness of the resection of acid secreting mucosa.

*Loss of triturating function.* The food of the gastrectomized dog must be ground. Large pieces of meat or boiled potato may traverse the alimentary tract practically unchanged. In the rat, pig and monkey the diet is naturally well masticated or is well comminuted.

*Loss of digestive function.* The factor of safety in digestion is large. Total gastrectomy obviously reduces it. The coefficient of digestion of boiled ground meat in normal dogs in our laboratory is approximately 95 per cent, whereas in gastrectomized dogs it varies from 60 to 80 per cent (3). Our results agree essentially with those of Emery (4). The alimentary tract of such animals is quite unstable. For example, raw ground meat, particularly if it contains considerable fat, may cause diarrhea. Recently we (3) attempted to determine the coefficient of digestion of cooked ham (lean portion) and found that it caused diarrhea in our gastrectomized animals. These animals are also sensitive to fat. Our experience with more than 50 gastrectomized dogs teaches that they require from 25 to 50 per cent more of a diet containing meat, milk and bread, for maintenance, than a normal dog.

When properly fed, gastrectomized dogs (1, 9), puppies (5), pigs (6, 11, 12, 13), and monkeys (7) remain in good condition. The pigs require iron, however, to remain in good condition and they do not grow and put on fat as well as a normal pig. One of the several that we kept for two years weighed 425 pounds. However, we have not been able to obtain a diet that will cause growth or maintain the preoperative weight in gastrectomized rats (8). In the rat

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the stomach appears to be an essential organ, but we are unwilling to draw such a conclusion until dietary factors have been more extensively studied.

*Hematopoietic function.* Since 1923 we (1, 5-8, 10) have attempted to produce the blood and bone-marrow picture of pernicious anemia in animals by gastrectomy and dietary modification. We have failed and have no faith in the few reports to the contrary that have appeared in the literature (11). We, as well as others (12, 13) have been unable to confirm the observations of Bence (11) on pigs, which are rather convincing, since we (6) and others (12) have found with Bence that the antipernicious anemia factor in the livers of gastrectomized pigs undergoes a marked diminution. In a few rats given iron parenterally, marked macrocytosis was observed, and in one a hyperplasia of the bone marrow was found, and it simulated somewhat that found in pernicious anemia (8). Hyperplasia of the bone marrow is commonly found in gastrectomized animals (1, 5, 7, 11), though hypoplasia may also be found (7, 8, 17). Anemia when present, as it is always in the rat and pig, unless treated with iron, is usually hypochromic, erythropenic and microcytic in type.

*Bacteriostatic and bacteriocidal function.* This function of the stomach has been established by the observations of Arnold (14). We have made no direct experiments on the subject. However, we have observed that gastrectomized animals are susceptible to enteritis (1) in the summer months. We have lost as many as three gastrectomized dogs from enteritis during a single one-week period of hot weather. This has not occurred recently because we have learned not to place all the daily ration in the food pan at one time.

*Absorption of iron.* Iron balance studies have not been made on gastrectomized animals. Dogs occasionally manifest a microcytic, erythropenic, hypochromic anemia (1, 10, 9, 15). A more severe anemia may be precipitated by intercurrent infection, prolonged diarrhea, pregnancy (1, 7, 16), or an inadequate diet (17). Gastrectomized dogs are deficient in their ability to regenerate hemoglobin, a deficiency that responds to iron but not to the antipernicious anemia fraction of liver (18). We cannot state with certainty that the anemia that appears in the gastrectomized dog under conditions of stress is due solely to a deficiency of iron absorption; yet, it appears to respond to iron therapy. In the monkey the anemia, when it occurs following gastrectomy, resembles that of the dog (7). The anemia of the pig resembles that of the rat, in which a complete return to normal levels is difficult to attain by the administration of iron (6, 8). Bussabarger and Ivy (19) have obtained a completely normal blood picture by giving a concentrate of liver protein (No. 55, Eli Lilly and Co.) with iron orally to a small group of gastrectomized rats. (This is now being studied further). The return of the blood to normal was not accompanied by a return of normal growth. Adequate protein digestion and absorption, as well as iron, is required for hemoglobin manufacture. We suspect that both are deficient in the rat and pig, since both animals were adequately supplied with abundant vitamins in their diet.

Radical subtotal gastrectomy in the dog, including all of Brunner's glands or the duodenum does not cause anemia (13, 22).

*Absorption of calcium.* When puppies are gastrectomized at an age of 2 or 3 months, a homogeneous osteoporosis results of such severity that gross deformities and spontaneous fractures of the bones of the extremities result. They do not develop rickets. The percentage composition of the bone laid down is normal, but too little is formed to support the weight of the growing animal. The condition is ameliorated but not completely prevented by the administration of soluble calcium salts. It was shown that soluble calcium salts are normally absorbed by the intestine of such animals. In adult gastrectomized dogs (5, 9) and pigs, the bones are decalcified, but not sufficiently to cause deformities and spontaneous fractures (5). We have seen one case of homogeneous osteoporosis in a human patient subjected to a radical subtotal gastrectomy.

Four observed factors contribute to the production of the osteoporosis (5). One is the absence of HCl which normally renders food calcium more soluble and available for absorption. The second is the loss of the reservoir function of the stomach, in the absence of which the food in an inadequately digested state is passed rapidly through the upper intestine, where most of the calcium is believed to be absorbed. The third factor is the presence of postcibal acidosis due to the secretion of alkaline juices and the absence of secretion of gastric juice. In the presence of acidosis the absorbed calcium is not normally deposited in bones and bones are decalcified. The fourth factor is the hyperplasia of the red bone marrow which encroaches on the osseous tissue.

## DISCUSSION

The differences observed between the reaction of the rat and pig on the one hand and the dog and monkey on the other in regard to anemia may be due to a true "species difference." However, we suspect that the difference is more likely due to the degree of success that has been attained in the search for an adequate diet. For example, one group of workers (20) has reported that gastrectomized puppies show marked changes in nutrition and gait, as well as changes in the skin and nervous system. The change in gait observed was due probably to osteoporosis, as noted above; and with our diet we have observed no changes in the mouth or tongue (1), in the skin (5), and nervous system. In fact we have observed no changes in the nervous system (8, 21), symptomatically and histologically proven, in at least 70 dogs, 50 rats, 15 monkeys, 25 puppies and 20 pigs, kept in the gastrectomized state from 6 months to 10 years. The monkeys, pigs and puppies were kept for 2 to 3 years.

Obviously the presence of diarrhea or mushy stools, especially if associated with rapid intestinal passage, will predispose to mineral, vitamin and protein loss, all of which are concerned in the genesis of the various disturbances observed in gastrectomized animals.

## SUMMARY

The observations on the effect of total gastrectomy in animals show that the stomach in the strict sense is not an essential organ. Other than serving as a reservoir, the stomach performs no essentially specific function that cannot be dispensed with. The rat may prove to be an exception to this generalization. The removal of the stomach, however, reduces the factor

of safety in digestion and places a strain on the motor, digestive and absorptive activities of the intestine. The "acid tide" that occurs after eating in gastrectomized and achlorhydric animals or patients places a strain on calcium storage by the body. In addition gastrectomy places a strain on the mechanism concerned in the absorption of iron, and predisposes to enteritis. It cannot be stated that total gastrectomy causes pernicious anemia, combined degeneration of the spinal cord, stomatitis and glossitis, in the rat (6 months to 1 year), dog (1 year to 12 years), pig (1 year to 3 years), or monkey (1 year to 2.6 years).

The stomach is more important in the economy of the growing than the adult mammal. It is more im-

portant in the pregnant female than in the male (dog). Proper nutritional care is indispensable in maintaining health in animals without a stomach and very probably in men and women similarly handicapped.

Subtotal gastrectomy handicaps the patient only to the extent that it reduces the factors of safety in digestion and absorption and that the reduction is not in time compensated for by hypertrophy of the gastric remnant and by favorable changes in the upper intestine. The extent to which acid is secreted post-operatively depends on the amount of acid secreting mucosa removed and the degree of the hypertrophy of the remnant.

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## The Problem of Gastrectomy and the Anemias\*

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IT is obvious that a decision to remove the stomach, either in part or as a whole, must at once be accompanied by a question as to the possible deleterious effects of such a procedure. Aside from the evident fact that removal of all or most of the stomach results in the loss of a capacious and efficient container and mixer of ingested food, it is pertinent to inquire as to whether any indispensable functions have been lost. Loss of peptic activity is presumably of little moment, inasmuch as the duodenal and pancreatic secretions contain adequate and readily available proteolytic enzymes. The reduction or complete loss of hydrochloric acid cannot be said to be unimportant, although it is clear that a very large number of individuals, especially in the later decades of life, are apparently free of any troublesome symptoms even in the face of long-standing achlorhydria. It is also true, however, that so-called gastrogenic diarrheas exist and are frequently controlled by the administration of hydrochloric acid. Of importance to this discussion is the fact, proven by various investigators, that in the ab-

sence of adequate gastric secretion of hydrochloric acid, ingested iron is not fully utilized in the maintenance of a normal hemoglobin level. Prior to the work of Minot and Castle there is little doubt that the anemia of patients with pernicious anemia was benefited, although not controlled, by the use of hydrochloric acid. Here, then, is one factor concerned in the maintenance of normal hematopoieses that is affected to a greater or lesser degree by removal of gastric tissue. The chief site of acid secretion is known to be in the body and fundus of the stomach, a region obviously concerned in most gastric resections. Indeed, one of the stated purposes of gastric surgery is to reduce or to remove entirely the acid-secreting portion of the stomach.

Castle's (1-4) demonstration of a factor in gastric secretion directly concerned with the normal maturation of red blood cells added another important gastric function that had previously been almost entirely unsuspected. This fundamental factor in gastric juice, the so-called intrinsic factor, is essential to the maintenance of normal blood formation, and its absence is now known to be directly responsible for the development of primary Addisonian anemia. For

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the most part, cases of so-called pernicious anemia show a lack of hydrochloric acid secretion as well as a loss of the intrinsic hematopoietic factor. But of the two factors, the latter is the more fundamental inasmuch as there are rare but authenticated cases of pernicious anemia unassociated with complete achlorhydria.

The establishment of this important function of the stomach has provided us with a much greater understanding of the problems of hematopoiesis and must of necessity enter into any consideration of the effects of gastrectomy, subtotal or complete. In the absence of all or most of the stomach, what effects must one anticipate on the problem of normal blood formation? Such a consideration underlies a large amount of careful investigation directed at establishing the site of formation of this antianemic factor of Castle. It will be of interest to review the important investigative work that has been done. Castle (1-4) in his original work in 1929 presented conclusive evidence that there is found within the normal stomach, during the digestion of beef muscle, some substance capable of promptly relieving the anemia of patients suffering from pernicious anemia. This substance was absent from the gastric secretion of patients with pernicious anemia. He further, apparently, showed that this "intrinsic factor" could not be demonstrated in normal human duodenal contents nor in saliva when either secretion was incubated with beef muscle. He concluded that this active constituent of normal human gastric contents is in all probability secreted by the gastric mucosa. For the first time a relationship between the stomach and the bone marrow was demonstrated, and the general belief that the integrity of the stomach is unnecessary to proper body metabolism was brought into question. Castle also showed that this antianemic factor was independent of the gastric secretion of acid, pepsin or rennin. His studies were made entirely on the gastric secretion of human beings.

Since these studies various investigators have sought to obtain more precise information as to the site of formation of this intrinsic factor. Sturgis and Isaacs (5) in 1929 showed that dried pig's stomach was efficacious in the treatment of pernicious anemia, as did Conner (6) and Wilkinson (7) somewhat later. Subsequently Meulengracht (8-13) carried out more detailed experiments, employing preparations of the cardiac, fundic, pyloric and duodenal mucosa from swine. No anti-anemic factor could be demonstrated in material from the fundus; maximal activity was noted in that obtained from the pylorus and from the duodenum; only slight activity was obtained after the use of cardiac tissue preparations. He concluded that the glands of the cardia and pylorus and Brunner's glands in the duodenum are functionally identical and that, in man, pernicious anemia is due to failure of the pyloric gland organ. By analogy with the pig, he assumed that the presence of Brunner's glands in man accounted for the fact that every gastric atrophy and every gastric resection does not develop pernicious anemia. Accordingly, following Meulengracht, the question as to whether a primary anemia will develop under such conditions will depend on the extent and functional activity of Brunner's glands in the duodenum.

In attempting to correlate his experimental results with autopsy findings in pernicious anemia, Meulengracht (14) found, as had Faber and Bloch (15) in 1900, that in man the greatest atrophy of gastric mucosa occurs in the fundus, whereas the pyloric glands and Brunner's glands are well preserved. Such a finding was at distinct variance with his experiments on the efficacy of various portions of pig's stomachs and necessitated the postulation of a hormone produced by the fundic glands necessary for the stimulation of the pyloric glands to secrete the antianemic factor found in gastric secretion.

Thompson (16), like Meulengracht, obtained excellent remissions in patients with pernicious anemia following treatment with the dessicated duodenal mucosa of swine. Uotila (17), similarly, noted satisfactory results following the use of powdered ileum, duodenum and jejunum, the first preparation being most potent.

Ivy and his collaborators (18) studied the effects of total gastrectomy in dogs and noted the development of hypochromic anemia in some animals. Pregnancy was uniformly associated with the production of such an iron deficiency anemia, and Shumacher and Wintrobe (19) observed the development of a hypochromic, microcytic anemia in totally gastrectomized dogs, which, in addition, had become ill with distemper. Total gastrectomy performed on swine, monkeys and rats as in dogs has been followed by normocytic, or microcytic, hypochromic anemia in all instances. Ivy showed, however, that the so-called intrinsic factor present in hog's stomach is more than twice as effective as that obtained from canine gastric tissue. There is, therefore, not only a striking difference in the antianemic potency of stomach preparations from different animal species, but as Ivy (20) points out, the dog, pig and rat appear to be so biologically constituted that they do not develop the blood picture of pernicious anemia. Animal experimentation so far, although of extreme interest as regards the development of an iron deficiency anemia after subtotal or total gastrectomy, has thrown no convincing light on the exact source of the antianemic factor demonstrated by Castle to be present in human gastric juice. It is still impossible to translate to man, except by analogy, the results obtained after gastric resection in the dog, swine, rat or monkey. It is important to point out, however, that in all the animal experiments anemia developed following gastric resection only after many months to years, except in the presence of other factors, such as pregnancy.

Two histo-pathological studies are of interest as suggesting that in man, also, the macrocytic anemia characteristic of Addisonian anemia does not develop unless there are important extragastric lesions existing in the digestive tract. Brown (21) showed what he interpreted as widespread evidences of enteritis in a large number of autopsy specimens from patients dying of pernicious anemia. Deductions from these studies are open to question, however, because of failure to fix the tissues immediately after death. Of much greater suggestive interest is the recent histological study made by Jacobson. Material from the stomach and intestines was obtained from various animals and from human cases dying from pernicious anemia, sprue and certain other diseases. Jacobson (22) points out the striking parallelism in the dis-

tribution of argentaflavine cells in man and in the pig and the localization of the principle active against pernicious anemia in the mucosa of the gastro-intestinal tract. In patients dying with pernicious anemia the argentaflavine cells, which normally are found in the cardia, pylorus, duodenum, small intestine, colon and appendix, are completely or almost completely absent throughout the gastro-intestinal canal. He suggests the interesting possibility that these particular cells are responsible for the secretion of Castle's intrinsic factor but admits that as yet convincing proof is lacking. In view of Castle's original failure to produce a remission in pernicious anemia patients fed a mixture of beef muscle incubated with normal human duodenal contents, caution is still necessary in interpreting Jacobson's suggestions. In spite of the lack of complete proof, it is obvious on the basis of animal experimentation that development of a primary Addisonian anemia in man as a sequel to partial or total gastrectomy is rarely to be expected. Clinical reports are fully in accord with such an assumption.

Moynihan (23) in 1911 reported a successful removal of the entire stomach for cancer in a patient whom he was able to follow for over three years. A severe anemia developed two years after operation, responded to treatment temporarily but subsequently recurred and resulted in the death of the patient. Autopsy showed no evidence of malignancy, and presumably the anemia was the cause of death. Following the report of this case, sporadic instances of macrocytic anemia occurring after gastric resection have appeared from time to time. In 1933 Goldhamer (24) was able to collect 23 cases from the literature, including one of his own. Since then not more than 10 cases have been reported, although without doubt more have occurred. In 1939, however, Sturgis and Goldhamer (25) were unable to collect more than 3 cases of macrocytic anemia following gastric resection from the preceding 11 years' total group of anemia patients seen by them at the Simpson Memorial. At least 271 patients, who had major gastric surgery in 6 different hospitals, were followed carefully during recent years (26-31) and no cases were noted to have developed a macrocytic anemia. Walton (32) was unable to record any such development in a group of almost 800 partial gastric resections, although the care with which this group of patients was followed is open to question. Among the individual cases reported, only one or two are believed to have developed sooner than two years after operation. Two cases, reported by Vaughan (33) and Heck and Walters (34) respectively, changed from hypochromic microcytic forms of anemia prior to operation to macrocytic anemias at a date long after gastric resection.

Mild hypochromic anemias following gastric surgery are not at all uncommon, and more severe grades are by no means rare. Fourteen per cent of a group of 117 patients subjected to subtotal or total gastrectomy at Mount Sinai Hospital and reported to this society in 1933 by Rosenthal (31) developed varying degrees of iron deficiency anemia over a period of from 6 months to 17 years after operation. An analysis of 40 cases of hypochromic anemia occurring after gastric surgery was made by Hartfall (35). Most of the cases were in women at or near the menopause. The severity of the anemia appeared to increase with its duration, and 25 of the 40 cases were on an obviously deficient dietary. In the most severe cases slight splenomegaly, glossitis and changes in the skin and nails were noted. The most severe cases followed a gastrojejunostomy. In keeping with the implications suggested above, Meulengracht (36) and Rowlands (37) stress the importance of the achylia gastrica type of syndrome occurring after radical gastric surgery, with the not infrequent associated phenomenon of an increased intestinal rate. Castle (1-4), Ivy (20) and others have pointed out clearly the importance of the interference to the digestive tract as a whole that may underlie the development of either the macrocytic or the more common microcytic anemias. Minot (38) has recently told me of a rather unusual type of anemia occurring after gastric resection—namely, a fairly severe normocytic normochromic anemia, responding neither to iron nor to liver therapy. Similar cases have apparently been fairly frequently noted and reported in continental European literature (39) but so far have not attracted much English and American attention.

It is apparent that major gastric surgery—subtotal or total gastrectomy—may be performed without any great fear of undue consequences as far as the factor of normal hematopoiesis is concerned. In spite of the fact that relative or absolute achlorhydria results and secretory cells of importance to normal blood physiology may be removed, the development of serious anemias need not be feared. An occasional severe microcytic or macrocytic anemia may ensue in the course of many months following operation. In all probability, however, such anemias are readily treated with iron or liver. Of more importance is the fact that in most instances intelligent post-operative dietary management, together with the administration of minimal amounts of iron and liver, constitutes a measure amply sufficient to prevent the occurrence of such complications. The search for the exact site of formation of the intrinsic antianemic factor must still be pursued, but in spite of our lack of accurate knowledge as to its source, proper gastric surgery need not be avoided.

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## Gastrosopic Observations in Resected Stomachs

By

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**G**ASTROSCOPY has enabled us to study extensively the anatomic aspect of the resected stomach. This paper is a report on 54 such patients in whom 204 gastrosopic examinations were carried out. In 40 patients only one examination was made; in 14 patients 164 gastrosopic observations became possible, the patients of this group having had an average of about 12 gastrosopies each.

The artificial stoma was usually well seen, and in 13 patients the jejunum was entered with the gastroscope, an observation of about 10 cm. of its mucosa thus becoming possible.

The artificial stoma after any type of gastric operation usually is patent and rigid (Fig. 1), but sometimes an automatic rhythmical pylorus-like activity—regular opening and closing with a stellar formation—may be seen, and I am inclined to believe that only if this automatic activity of the stoma is present, the condition of the resected stomach can be called a rather physiological one. This observation, in my opinion, is of great practical importance; but we do not know how this result may be obtained. Continued animal experiments should further our knowledge of this important point.

The majority of patients with resected stomachs are seen at gastrosopy because they have serious distress. They may warp our judgment of the incidence of recurrent trouble after resection. In our series, how-

ever, many of the patients were examined as a routine procedure.

11 patients had had a resection for gastric carcinoma, 41 for gastric or duodenal ulcer, 1 for hyperplastic-atrophic antrum gastritis, and 1 for gastric syphilis.

None of the 11 patients whose stomach had been re-

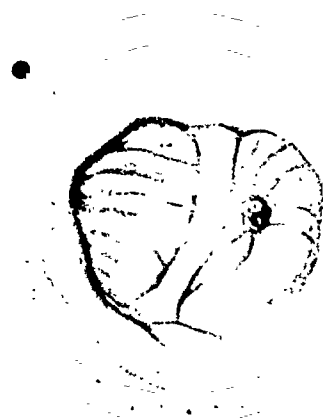


Fig. 1. Gastrosopic picture of a patent stoma after resection. The entire circumference of the stoma is seen. Both loops of the jejunum are visualized. They are characterized by their Kerkring folds. The spur is seen between them. The posterior loop shows a peristaltic wave almost closing its lumen.

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sected for carcinoma (see Table I) had a normal gastric mucosa at gastroscopic examination. In 5 cases recurrence of the carcinoma was seen (Fig. 2); once severe purulent acute gastritis (Fig. 3) was observed, three weeks after the resection—a common finding such a short time after any gastric operation; and 5 times chronic gastritis of the superficial-atrophic type was found.

TABLE I  
*Gastric mucosa after resection for carcinoma (11 cases)*

Gastroscopic Findings	Number of Cases	Remarks
Normal	0	
Recurrence	5	One case with marginal ulcer. One case with severe gastritis.
Purulent acute gastritis	1	3 weeks after operation.
Superficial gastritis	2	One case 1½ years after resection.
Superficial and atrophic gastritis	1	
Atrophic gastritis	2	One case of complete atrophy 10 years after resection.
Total	11	

Table II demonstrates the gastroscopic findings in 41 patients in whom a resection for ulcer had been made. In only 4 of them a perfectly normal mucosa was seen. In these four patients (and in no other patients!) was found the rhythmical automatic pylorus-like action of the stoma. In one case a recurrent ulcer of the lesser curvature was found; it is likely that this was caused by the presence of a silk thread which had cut through the mucosa. In 5 cases marginal or jejunal ulcers (Fig. 4) were observed; in one of these cases severe atrophy of the gastric mucosa was present. Silk threads may cut through the mucosa and not be eliminated for many weeks. They may cause

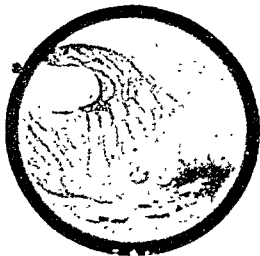


Fig. 2. Gastroscopic picture of a resected stomach. In this patient a gastric carcinoma was removed by resection eleven years prior to the gastroscopic examination. The blind end of the stomach is seen as a kind of pouch in the left upper quadrant. The tumor-like prominence seen in this region is a pseudopolyp made at the surgical interference and has no practical significance. An anterior gastro-enterostomy is present in the right lower quadrant. At its anterior margin two small erosions are noticed. The stoma opened and closed rhythmically, ejecting with every contraction pieces of necrotic material into the gastric cavity, which accumulated in its lowest portion. Four such necrotic pieces are seen in the gastroscopic field. The diagnosis of a recurrent carcinoma in the intestine below the stoma was made according to this observation, and this diagnosis was confirmed by laparotomy.

ulcerations and inflammation by continuous friction and may require surgical removal (Fig. 5). Such free silk threads were encountered in 6 cases; in one of them a recurrent ulcer was present, in another a marginal ulcer. 4 were combined with gastritis or jejunitis. Chronic gastritis (Fig. 6) and jejunitis is by far the most frequent disease of the resected stomach. In our material it was found in 27 cases.



Fig. 3. Gastroscopic picture of severe, acute, purulent, erosive gastritis, observed two and one-half months after resection. The rather normal jejunum is seen in the left upper quadrant. The gastric folds are tremendously swollen, and edematous. Between them purulent secretion is present. Two erosions are seen at the bottom of the picture.

This, not the rarer marginal ulcer, is the disease which threatens to spoil the results of gastric resection. In my experience the significance of the symptoms of this important disease usually is underestimated by the surgeon. Nevertheless it is this condition which may stifle our present enthusiasm for gastric resection for ulcer.

The resection for hyperplastic-atrophic antrum gastritis with pyloric obstruction proved to be very satisfactory. The many small scars seen in a stomach resected for syphilis probably were the result of treated gummas.

TABLE II  
*Gastric mucosa after resection for peptic ulcer. (41 cases)*

Gastroscopic Findings	Number of Cases	Remarks
Normal stomach	4	In all 4 cases (but only in these 4 cases) rhythmical action of the stoma.
Recurrent ulcer	1	Combined with silk threads.
Marginal and jejunal ulcer	5	Often combined with gastritis, in one case with severe atrophy.
Silk threads hanging loosely into the cavity	4 (and 2)	4 combined with gastritis and jejunitis. 1 with recurrent ulcer. 1 with marginal ulcer.
Gastritis: Mixed types: complete atrophy	15 5	
Jejunitis	1	Erosive jejunitis without gastritis.
Gastritis and jejunitis	6	
Total	41	

The constantly changing anatomic aspect of a resected stomach can be appreciated only by repeated gastroscopic observation. Then we find silent marginal ulcers, leading to unexpected massive hemorrhage, or we find a jejunal ulcer as the cause of continuous distress. We may find severe gastritis, the probable reason of great weakness, serious abdominal dis-



Fig. 4. Gastroscopic picture of a marginal ulcer in a resected stomach. Eleven days before this gastroscopy a severe gross hemorrhage had occurred. The jejunum is seen in the right side of the picture. The cavity of the stomach appears in the left lower quadrant. The suture line between the stomach and the jejunum is elevated and contains a round ulcer, which at gastroscopy was brilliant and yellow in color. In the center of this ulcer a dark brown spot is seen which has to be interpreted as a thrombus in a blood vessel.

comfort, etc., but often being entirely symptomless for a long period of time until suddenly symptoms reappear. The anatomic gastric history of a patient, gastroscopied 40 times from 1934 to 1940 is demonstrated in Table III. A deep jejunal ulcer healed; mild inflammation was seen. A massive hemorrhage was unexplained. Time and again ulcerations were formed and disappeared. Sometimes only mild jejunitis and gastritis was observed. After a gross hemorrhage the most unusual picture of a thrombus in the depth of the floor of a marginal ulcer was observed (Fig. 4). Table IV shows the findings in a patient gastroscopied 34 times. In the beginning severe gastritis was seen. Three years later a marginal ulcer was found and three weeks after this observation a gross hemorrhage occurred. At present this stomach shows no pathology at all. Another patient, referred to in Table V, having continuous distress after resection, presented the most severe types of gastritis, at first superficial, later atrophic in character. 15 gastroscopies were made. Table VI gives the results of 14 gastroscopies carried

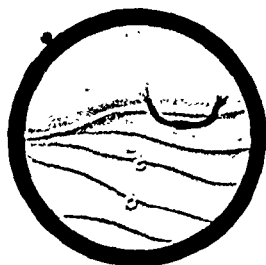


Fig. 5. Gastroscopic picture of the gastric mucosa of a resected stomach in the surroundings of the stoma. A blackish silk suture has cut through the mucosa and it is hanging freely into the gastric cavity.

out in a patient who after the resection developed a severe gastritis and jejunitis which before the resection had not been present. Evidently the purulent post-operative gastritis had become chronic. In another patient 23 gastroscopies were performed before the resection in order to observe the course of a gigantic ulcer. At that time only mild gastritis was present. But after the resection (Table VII) the usual severe purulent gastritis developed, which in this case unfortunately turned into extensive atrophy. The very rare case of an erosive jejunitis with subsequent scar formation is illustrated on Table VIII. Therapy of this case was eminently successful. He had had a duodenal ulcer, a gastro-enterostomy, a gastrojejuno-colic fistula, and a resection; and then the erosive jejunitis developed. It healed almost completely after high voltage X-ray therapy.

It is evident that repeated gastroscopic examinations of the resected stomach reveal a multitude of varying

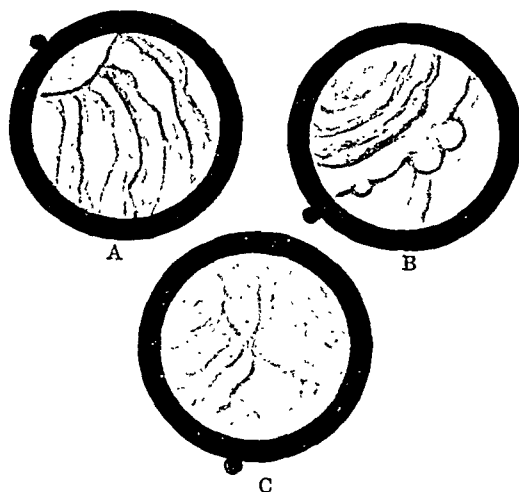


Fig. 6. Three gastroscopic pictures seen in the same resected stomach. A. Here the gastroscope has entered the jejunum. The jejunal folds are close to the objective. No definite pathology is present. B. The gastroscope has been withdrawn into the stomach. The jejunum is still seen in the left upper quadrant. The suture line shows several "pseudopolyps," all of them caused by the suturing and having no practical significance. C. The gastric mucosa is thoroughly atrophic, greenish-gray in color, and so thin that the submucosal blood vessels, normally invisible, can be seen.

anatomic changes, as described in this paper. They should be familiar to the surgeon as well as the gastroenterologist.

## DISCUSSION

DR. A. F. R. ANDRESEN (Brooklyn, N. Y.): I should like to accept the gauntlet that was thrown down that the patients who are operated upon and have subtotal gastrectomy done for ulcer are the ones who were failures of medical treatment. I wish to emphasize a thing I have said here many times before, and that is I don't believe there is any medical treatment for ulcer—that an ulcer heals spontaneously. It is a part of every history of ulcer that spontaneous remissions occur, that all evidences of ulcer disappear in the interim. A simple, uncomplicated ulcer therefore requires no specific medical treatment—the treatment is palliative and symptomatic.

If we would only pay a little less attention to acid values in ulcer, either from the medical or surgical viewpoint, we



would get better final results from our care of ulcer patients. If we would pay more attention to prevention of recurrence of ulcer by looking after the general condition of the patient, by removing infections and allergic factors, and by taking care of complications which prolong the

TABLE III

*Gastrosopic observations in patient No. 6167 having had a resection for duodenal stenosis.*

6167 8-31-33—RESECTION FOR DUODENAL STENOSIS

1	10-27-34	Patent stoma. Small area of hemorrhagic inflammation.
2	12- 7-34	Deep jejunal ulcer crater. Purulent jejunitis and gastritis.
3	12-13-34	Jejunal ulcer. Inflammation improved.
4	1-30-35	Ulcer shallow. No jejunitis. No gastritis.
5	3- 5-35	No ulcer. No inflammation.
6	4- 3-35	No ulcer. Slight gastritis.
7	5- 2-35	Jejunal erosion. No inflammation.
8	7- 5-35	Jejunitis.
9	11- 5-35	Only mild inflammation.
10	1- 4-36	Mild inflammation.

3-26-36—MASSIVE HEMORRHAGE

11	7-17-36	No pathology.
12	10-28-36	Jejunal ulcer, 1 cm. below stoma.
13	12- 9-36	Gastritis and jejunitis.
14	1- 6-37	Very mild gastritis.
15	2-10-37	Residue of gastritis.

3-13-37—GROSS HEMORRHAGE

16	3-24-37	Marginal ulceration (with thrombus in center).
17	5-12-37	Jejunitis.
18	9-20-37	Jejunum entered. Jejunitis and gastritis.
19	10- 4-37	Ulcerative gastritis.
20	10-25-37	Only mild inflammation.
21	12- 6-37	Small erosion in jejunum. Gastritis.
22	1-10-38	Purulent ulcerative jejunitis and gastritis.
23	2- 7-38	Almost no pathology.
24	5-18-38	Purulent jejunitis.
25	6- 8-38	2 marginal erosions. Jejunitis and gastritis.
26	6-28-38	2 marginal ulcers.
27	7- 8-38	2 marginal ulcers.
28	7-25-38	2 marginal ulcers. Slight gastritis.
29	9- 2-38	Marginal ulcer. Jejunitis and gastritis.
30	9-30-38	Jejunitis and gastritis (1 erosion?)
31	10-29-38	Marginal ulcer. Gastritis.
32	12-12-38	Marginal ulcer. Slight gastritis.
33	1- 7-39	Marginal ulcer healed. Marked gastritis.
34	4-10-39	No gastritis.
35	6-14-39	Gastritis.
36	8-16-39	Jejunal and marginal erosions.
37	11-10-39	Marginal erosions. No gastritis.
38	12-22-39	Slight jejunitis.
39	2-23-40	Marginal ulcer. Mild gastritis.
40	3-18-40	Marginal ulcer. Mild gastritis and jejunitis.

duration of the ulcer, we wouldn't have to be stigmatized as being failures in the treatment of ulcer.

Too often the persistence of symptoms is made the excuse for operation for ulcer, without attempting to make a complete diagnosis. Persistence of symptoms in ulcer may be due to complications elsewhere which are causing ulcer symptoms, even though an ulcer has previously been shown to be present. It may be due to allergic irritation, some food causing irritation and persistence of the ulcer. I believe the persistence of symptoms for which operation is indicated is due to a very definite complication in the ulcer in practically every case.

The ulcer that the surgeon sees and in which he says medical failures have occurred, is the complicated ulcer,

TABLE IV

*Gastrosopic observations in patient No. 71389 beginning two years after gastric resection*

71389 1928—GASTRO-ENTEROSTOMY  
1933—RESECTION (JEJUNAL ULCER AND GROSS HEMORRHAGE)

1	5-11-35	Severe gastritis of post-operative stomach.
2	5-14-35	Severe hypertrophic ulcerative gastritis.
3	7-15-35	Severe gastritis.
4	10-31-35	Gastritis improved.
5	1-22-36	Edematous inflammation of stoma edge.
6	3-18-36	Both loops seen. Pseudopolyp. Edema of stoma.
7	5-18-36	Only mild gastritis.
8	10-14-36	Slight residue of gastritis.
9	12-10-36	Definite gastritis.
10	1-20-37	Rather normal mucosa.
11	3-24-37	Again chronic gastritis.
12	6- 2-37	2 erosions at stoma. Pseudopolyp. Mild gastritis.
13	9- 6-37	No pathology.
14	12- 1-37	Erosions at the stoma. Gastritis.
15	1-12-38	Gastritis.
16	3- 7-38	4 small shallow jejunal ulcers. Extensive hypertrophic gastritis.
17	3-29-38	Mild jejunitis and gastritis.
18	5-23-38	Marginal ulcer and marginal erosion. Slight gastritis.

6-14-38—SEVERE GROSS HEMORRHAGE

19	7- 6-38	Severe ulcerative gastritis.
20	7-20-38	No pathology.
21	8-24-38	Mild gastritis.
22	9-28-38	Marginal ulcer (silent).
23	10-22-38	Jejunitis and gastritis.
24	11-16-38	Normal mucosa.
25	12-21-38	2 jejunal superficial erosions. Gastritis.
26	2- 1-39	One tiny marginal erosion. Jejunitis and gastritis.
27	3- 2-39	Extensive shallow erosion of anterior loop.
28	4- 5-39	Marginal erosion.
29	6-19-39	No pathology.
30	8-21-39	No pathology.
31	9-25-39	Small area of hypertrophic gastritis.
32	10-23-39	Mild jejunitis. No gastritis.
33	12-18-39	Jejunitis of posterior loop.
34	2-14-40	No pathology.

the deep, indurated ulcer which has either perforated or reached the peritoneal surface, causing adhesions to neighboring organs, marked induration and deformity with more or less stenosis, occasionally with hemorrhages due to the enclosure of a bleeding vessel in a hard mass of horny induration. In the case of such complications, the internist who takes care of the case should recognize those which are not going to disappear spontaneously during medical care and then these patients should come to operation earlier. I agree entirely with the more radical procedures in such cases. The cases that the surgeons have shown us here were all cases in that class, and I object to their being called failures of medical treatment. They should have received medical treatment only in preparation for operation.

In hemorrhage it has been shown the lowest mortality occurs in patients fed early, in whom transfusions have

TABLE V  
*Gastroscopic observations in patient No. 200924 beginning two years after gastric resection*

200924	1933—GASTRIC RESECTION
1	5-27-35 Unusually severe gastritis with 1 marginal erosion.
LAPAROTOMY—No pathology at palpation. Abdomen closed.	
2	6-28-38 Unusually severe gastritis, mostly of superficial type.
Attempt of X-RAY THERAPY of stomach from 7-21-38 to 8-13-38: 2,268 R.	
3	8- 3-38 Still gastritis.
4	8-22-38 Severe superficial gastritis.
5	9- 9-38 Severe superficial gastritis.
6	10- 7-38 Perhaps beginning atrophy.
7	11- 2-38 Superficial gastritis improved.
8	12-14-38 Again very severe gastritis.
9	1-12-39 Again very severe gastritis.
10	6-12-39 Severe gastritis, now almost exclusively atrophic in character.
11	7-10-39 Extensive atrophic gastritis.
12	8- 9-39 Extensive atrophic gastritis.
13	9-25-39 Atrophic hemorrhagic gastritis.
14	10-26-39 Atrophic gastritis.
15	3- 4-40 Severe atrophy with overlapping superficial gastritis.

been absolutely avoided except in the greatest of emergency, and in whom the application of cold to the exterior or interior of the stomach has been avoided. Mortality in such cases, in various reports has been brought down to somewhere in the neighborhood of 2 per cent, varying from 1.8 to 2.5%. Operation is rarely necessary and usually unsuccessful.

I think the most important factor in the operative care of patients either for carcinoma or for ulcer is proper and adequate pre-operative and post-operative care. As Dr. Lahey stressed in his paper, pre-operative care, proper diet, with adequate vitamin and transfusions, bringing the patient up to the proper condition for operation is very important. I think it is little short of murder to operate upon a patient who is dehydrated, who has a marked alkalosis, or a marked anemia. Such patients should not come to surgery until that condition has been corrected.

And post-operatively I think we have a very important duty to perform as internists and that is, we should start

our feedings on these patients immediately after operation. We have had our best results in the patients who have been started at once with feedings similar to those we use in gastric hemorrhage, with proper attention to vitamin content, and the avoidance of too much injection of fluid. That has been overdone and I think the pendulum is swinging away from this water-logging of the patient with sugar and salt solutions after operation and the use of too many drips or enemata and excessive sedation.

DR. WALTER L. PALMER (Chicago, Ill.): I think it would be of interest if Dr. Lahey would tell us briefly something of his indications at the operating table for carrying out resection in gastric carcinoma, and also what he thinks should perhaps be the optimum mortality rate

TABLE VI  
*Gastroscopic observations in patient No. 111438, the first gastroscopy being made after a posterior gastro-enterostomy and a few days before gastric resection, and the following thirteen carried out after resection*

111438	1926—POSTERIOR GASTRO-ENTEROSTOMY 1930—PERFORATION OF STOMACH 3 GROSS HEMORRHAGES	
1	9- 6-34	Shallow marginal ulcer.
9-12-34—RESECTION		
2	11-28-34	Extremely severe, <i>acute, edematous, erosive, hemorrhagic gastritis</i> . No jejunitis.
3	12-12-34	Still hemorrhagic gastritis.
4	1-29-35	Severe gastritis.
5	5-28-35	Jejunitis. No gastritis.
6	7- 1-35	Jejunitis improved.
7	10-23-35	Chronic gastritis.
8	3-21-36	Severe gastritis.
9	7-18-36	Severe erosive gastritis and jejunitis.
10	6- 4-38	Gastritis and jejunitis.
11	11-16-38	Mild gastritis of lower portions.
12	6-17-39	Mild gastritis.
13	9-30-39	Gastritis and jejunitis worse again.
14	12- 9-39	Inflammation less marked.

TABLE VII  
*Gastroscopic observations made after gastric resection in patient No. 173277. This patient had had twenty-three gastroscopic examinations between 4/28/37 and 6/25/38 because of gigantic benign gastric ulcer, accompanied by only mild gastritis*

173277	6-25-38—RESECTION
1	7-11-38 16 days after resection tremendous acute gastritis.
2	8- 8-38 Acute gastritis much improved. Mild gastritis. Silk suture migrating through mucosa.
3	10-31-38 Jejunum entered. Severe erosive jejunitis. Beginning atrophy of stomach.
4	12- 7-38 Jejunitis and gastritis. Silk threads of stoma having cut through the mucosa.
5	1-10-39 Gastritis.
6	4- 5-39 Silk thread hanging freely into gastric cavity. Mild gastritis.
7	6-16-39 Definite atrophy of stomach.
8	9-29-39 Inflammation around stoma. 2 marginal ulcerations. Extensive atrophic gastritis.

of carcinoma. I have in mind the fact that if one resects only the most favorable cases, the mortality rate of operation obviously is rather low; whereas, if one attempts to resect all cases, the mortality rate becomes quite high. Somewhere in between there must lie a middle ground and

TABLE VIII  
*Gastroscopic observations in patient No. 130626. This patient had had a gastro-enterostomy because of duodenal ulcer in 1930. A gastrojejunocolic fistula developed, and the gastro-enterostomy was closed. In 1936 a recurrent duodenal ulcer was found, and on 4/29/36 a gastric resection was performed.*

130626		4-29-36—RESECTION
1	8- 5-36	Severe erosive jejunitis (unique case). Jejunum entered.
2	9-23-36	Marked erosive jejunitis. Marginal ulcer.
3	11-27-36	3 jejunal erosions. Gastritis.
4	12-16-36	Chronic erosive jejunitis. Chronic hypertrophic gastritis.
5	12-23-36	Chronic erosive jejunitis. Chronic hypertrophic gastritis.
6	1- 6-37	Chronic erosive jejunitis. Chronic hypertrophic gastritis.
7	1-21-37	Chronic erosive jejunitis much improved. 2 erosions of stoma. Hypertrophic gastritis.
8	2- 3-37	Erosive jejunitis.
9	4-28-37	Erosive jejunitis. 1 pigment spot.
10	5-12-37	Erosive jejunitis much improved. Hypertrophic gastritis.

High voltage X-RAY THERAPY of stomach from 6-2-37 to 6-12-37: 2,990 R.

11	6-16-37	Erosive jejunitis. Gastritis improved.
12	7- 5-37	Erosive jejunitis healed.
13	9- 1-37	No pathology. As usual 10 cm. of both loops of the jejunum were visualized.
14	9-29-37	No jejunitis. Mild gastritis.
15	12-15-37	No jejunitis. Mild gastritis.
16	2-16-38	No jejunitis. Mild gastritis.
17	3-30-38	Marked scar of jejunum with converging folds (unique observation).
18	5-25-38	Scar of jejunum. Mild gastritis.
19	7-28-38	Mild jejunitis and gastritis.
20	8- 3-38	Mild jejunitis and gastritis.
21	8-24-38	Scar of jejunum with surrounding inflammation.
22	10- 5-38	Scar. Inflammation worse.
23	11-16-38	Scar. Inflammation improved.
24	12-14-38	Scar. Inflammation improved.
25	2- 1-39	Scar. No inflammation.
26	4- 5-39	Scar. Mild inflammation only of the stoma.
27	6-14-39	Scar. Mild inflammation only of the stoma.
28	8-16-39	Small jejunal ulcer at edge of old scar.
29	8-31-39	Small ulcer healed. Mucosal hemorrhage in jejunum. Scar.
30	10- 6-39	Scar. Slight gastritis.
31	10-25-39	Mild jejunitis and gastritis.
32	11-15-39	Scar. Mild jejunitis and gastritis.
33	12-19-39	Scar. Perhaps beginning atrophy of fornix.
34	2-10-40	Scar. Mild gastritis.

I would like to hear what he considers to be the middle ground.

Dr. Berg didn't tell us how many cases of ulcer there were from which this group of 135 selected for operation. I should be interested in hearing that.

I shall not defend the medical treatment or the medical failures. I think Dr. Winkelstein ought to do that, because it seems to be quite a large group. I was surprised to find only thirty high grade obstructions. Why were the other hundred operated on?

I agree with Dr. Andersen that one should not operate on patients with dehydration and severe alkalosis. I, therefore, object to Dr. Berg taking out the five who were operated on at that time, because, as Dr. Andersen pointed out, dehydration and alkalosis can be so readily overcome by the administration of fluids. The so-called nephritis disappears in the course of a few days. It is not a matter of nephritis but decreased renal function. As the alkalosis is corrected, the blood urea nitrogen returns to normal and the renal function returns to its previous level.

I think the mortality rate could be improved.

DR. ASHER WINKELSTEIN (New York City): Concerning Dr. Berg's indications for the operation of partial gastrectomy, judging from his report, he operated on many of his cases because of chronic, intractable pain.

The sine qua non for the surgical cure of the peptic ulcer is the establishment of a post-operative achlorhydria. That occurs in gastric ulcer practically invariably, so that partial gastric resection for gastric ulcer is a cure. In duodenal ulcer, however, half of the cases still have acid post-operatively. In the ones with high pre-operative acidity (from 70 to 100) 75% will still have free acid post-operatively, and it is in that group you get the recurrent ulcers. Inasmuch as recurrent ulcers do not occur if there is a post-operative achlorhydria it is the problem of the surgeon to operate the duodenal ulcer patients with high pre-operative acidity, so that he will get post-operative achlorhydria without recurrences.

Despite Dr. Berg's optimistic outlook, we feel that in the general wards of any hospital there will be an appreciable number of recurrences after partial gastrectomy for duodenal ulcer in the cases with high pre-operative acidity.

Our solution to that problem is the addition of subphrenic anterior vagotomy to the resection. This is followed in most of the cases by post-operative achlorhydria without recurrence.

I should like to ask the surgeons about their experience with the Finsterer exclusion operation. We have found that the pre-pyloric exclusion operation for deep duodenal ulcer is unsuccessful.

We agree for the most part with Dr. Abell's remarks. However, gastro-enterostomy for aged people is not a very good operation. In the last few years we have seen several recurrences (jejunal ulcers) in old people. We are opposed to operation during an acute massive hemorrhage on account of the high mortality. It is better to operate when the hemorrhage has subsided and the patient is in good condition.

Dr. Jones, I selected thirty patients with true achlorhydria after partial gastrectomy for ulcer and saw them for ten years or more. None of them developed an anemia.

Dr. Ivy, we have no evidence either from the X-ray examinations or secondary operations of hypertrophy of the stomach after resection for ulcer in the human. That may be due to the very wide anastomoses usually made by the surgeon.

Dr. Schindler, there is the possibility that post-operative gastritis may have a beneficent aspect also. We have observed that a large number of our patients gradually lose the gastric acidity over a period of years. This is of great value in the prevention of post-operative recurrences.

DR. ROBERT ELMAN (St. Louis, Mo.): Mr. President, Ladies and Gentlemen: Our experience in St. Louis at the Barnes Hospital, in lowering the mortality of gastrectomy has been similar to the experiences expressed this morning. Undoubtedly, of course, much of this is due to improvements in technic; however, I think that much credit is due our biochemical colleagues.

There is one important point of view in regard to the preparation of patients, and the post-operative care which I would like to emphasize, i. e.

The necessity for an accurate correction of the deficiencies in the patient which have resulted from the disease for which gastrectomy is advised, or as a result of the trauma induced by the operation. Dr. Andresen has emphasized a few of these points and I should like to add to his emphasis that the replacement of electrolyte and of water, may be too enthusiastically followed; we must, therefore, realize not only what the deficiency is but also how much is required for replacement.

At the meeting of the American Surgical Society in St. Louis a month ago, I reported observations on patients with various types of gastro-intestinal operations in whom a tremendous amount of nitrogen was excreted into the urine immediately after the operation. The magnitude of this loss of nitrogen was great. For example, it might be translated into the terms of pounds of protein tissue lost by the patient, and in many of our cases as much as a pound and a half of protein tissue was lost per day following the operation.

Obviously this leads to a protein deficiency which must be met just as a deficiency in water and electrolyte. If the deficiency can be met by the ingestion of protein by mouth, so much the better. In many of these patients, at least for a few days after operation, especially those with peritonitis, oral administration is undesirable or impossible, and in these patients we have found that the intravenous injection of a complete mixture of amino-acid obtained by hydrolyzing casein, was not only able to cover the loss of nitrogen in the urine, but in many instances resulted in an increase of the serum protein or in a prevention of the fall in serum protein which sometimes occurs in these cases, as well as in an obvious clinical improvement in the patient's general condition.

I would like to emphasize more and more the biochemical approach in the preparation as well as in post-operative care of these patients, so we may look forward to the time when we can replace parenterally all of their nutritional deficiencies; gastrectomy may then be followed by an even lower mortality than we have at present.

DR. H. NECHELES (Chicago): Mr. Chairman, Members of the Society and Guests: We have studied a group of subtotal gastrectomies for a number of years following operation and have tried to correlate clinical and laboratory findings in these patients.

Complete blood counts, hemoglobin, size of the stomach and emptying time, gastroscopy, first done by Dr. Schindler, and later by myself, acidity, blood chemistry, and so on were performed. Of all these tests only two findings were remarkable: In practically all patients that had improved, a gain in weight was found—if the patient gained weight, he had no complaints. If the emptying time of the stomach following operation was between one and one and a half hours, the results were usually clinically satisfactory; if the emptying time was very short, in some patients it was ten or fifteen minutes, the results were not as good, but frequently the emptying time was prolonged later, and the patients felt improved.

Concerning acidity, we convinced ourselves that simple aspiration does not give a true picture of gastric acidity. One has to use constant suction.

Following section of one or both vagus nerves, gastric acidity returns. Contrary to the findings of Dr. Winkelstein we have seen frequently a decline of gastric acidity following operation and subsequent gastritis. As the gas-

tritis diminished, a gradual return of acidity was found in a number of patients. Administration of hydrochloric acid seems to be beneficial in a number of patients because it apparently diminishes the bacterial invasion of the stomach which accompanies gastritis.

DR. LOUIS E. BARRON (Boston): In 1935 we performed anterior abdominal vagotomy in an attempt to ameliorate certain gastric motor disturbances which occurred in a patient with vagotonia. The results of these studies were reported before this society in 1937. Observations were also made on the influence of vagotomy on gastric secretion. The pre-operative acidity was high. The results of this investigation revealed that vagotomy did not lower or alter in any way the gastric acidity in response to histamine.

Vagotomy, either alone or in combination with other gastro-intestinal procedures has been utilized in the management of functional as well as organic diseases of the stomach. Varying results have been reported. Birchers, in 1920, performed vagotomy for peptic ulcer, and reported a reduction in acidity associated with good clinical results. Latarjet, Gianolla and Pieri confirmed these observations. Schiassi performed vagotomy alone and in conjunction with gastro-enterostomy for peptic ulcer, He, too, reported excellent results. However, other investigators, notably Steinthal could not confirm these findings. Shapiro and Berg performed subtotal gastric resection associated with bilateral vagotomy in dogs and concluded that there was no experimental proof or convincing clinical evidence to support the hypothesis that subtotal gastrectomy even combined with vagotomy was the operation of choice for the surgical cure of peptic ulcer in man, on the basis that it provides a permanent lowering in gastric acidity.

Our results substantiate the view that vagotomy alone does not lower the secretion of hydrochloric acid.

PROFESSOR BORIS P. BABKIN (Montreal): I want to say a few words about vagotomy and acidity. It is true that after vagotomy the acidity of the gastric juice may not be diminished, but the volume of juice may. In such cases a small amount of highly acid juice will not do much harm, and subtotal gastrectomy and vagotomy will achieve their aim of diminishing the acidity of the *gastric contents*. Therefore in the post-operative period after the above-mentioned operations it is necessary to study not only the acidity of the gastric juice, but also its volume. Only then can a proper appraisal of the effect of vagotomy be made. We know very little concerning the effect of section of different branches of the gastric vagus on the volume and composition of the gastric secretion. However, after such sound clinical observations as those of Dr. Berg and Dr. Winkelstein, who showed that section of the anterior gastric branches of the vagus diminishes the gastric acidity, why should not this operation be performed? It will do no harm and will be of benefit to the patient.

DR. IRVIN ABELL (Louisville): In closing my part, I should like to report an experience somewhat similar to that reported by Dr. Mateer.

Since the preparation of this paper, we had a patient brought in with his first hemorrhage, a man sixty years of age, who within the last few months had suffered a rather severe coronary occlusion. When he entered the hospital, he had a hemoglobin of 30 and a red cell count of 1,600,000. Repeated transfusions apparently did no good because his red cell count went still lower, to 1,400,000, and it occurred to us to try his prothrombin clotting time. Finding that increased, we gave him the thyloguinone. The bleeding stopped and we were able to bring the count up to a level of 4,000,000 shortly.

Subsequent examination showed a duodenal ulcer. This experience, with that reported by Dr. Mateer, offers oppor-

tunity for one, at least in some few instances of hemorrhage from ulcer, to control it by this means.

DR. A. A. BERG (New York City): I am sorry that I offended Dr. Andresen and Dr. Palmer by saying that my cases represented 173 medical failures. Now, I have no discussion with Dr. Andresen about the curability of ulcer. I stated that these patients were referred to me, after prolonged medical treatment had failed to bring relief from the symptoms. I stated that everything that the dietician, everything that the internist, everything that the biochemist, everything that the infusionist and transfusionist could do to relieve these patients, had been done, and only when all the therapeutic means had failed to bring relief, were they referred to the surgeon for operative cure. Would Dr. Andresen call these cases medical successes or medical failures?

As to Dr. Palmer's objection to my placing the five deaths from tetany and alkalosis in a separate group, there is this to be said. When a patient suffering with an ulcer that has resisted all therapeutic measures at our disposal for bringing about relief, asks the surgeon, what are the risks of operation, he is not interested to know the risks of one of the worst complications of ulcers, namely, complete pyloric stenosis with tetany and alkalosis, dehydration and chronic tubular nephritis, none of which conditions he has I stated in my paper that in this series, there were twenty-nine cases of complete pyloric stenosis with five deaths from tetany, etc. and I put these five deaths in a separate heading. The question may be asked why tetanic dehydrated, alkalotic patients were operated upon. I think Dr. Andresen said that it was little short of murder to operate upon such cases. Would Dr. Andresen let them all die without an attempt to save them? There were twenty-nine of these complete pyloric stenosis cases in this series, would Dr. Andresen let them all die! I hope Dr. Andresen will acquaint us very shortly how he would treat this class of cases. At all events, the surgeon can only be accused of accessory murder. The premeditated murder lies at the doorstep of those internists who permit their patients to get into such a deplorable state, in which only the "Hand of the Almighty" could save them. I might also add that two of these patients had been treated by an eminent gastro-enterologist before they were referred to me by him.

Now as to the nine cases of repeated and repeated massive hemorrhages from ulcer, I do not mean just bleeding, I refer to patients who every day for ten days or more vomit basins full of blood. I have refused operation in a number of such cases and they have all gone to join their Maker. Now, in these nine cases that I reported here this morning, four of them died; five of them got well. Is it nothing to save five out of nine patients, who would all, surely—if we have any clinical judgment—have gone to join their Maker?

In regard to the question of vagotomy, and the experiments of Dr. Benj. Berg—by the way, this work was not mine—on experimental vagotomy and gastric secretion. Most of the clinical work that has been done on vagotomy has been a supposed division of the vagus nerve in the gastro-hepatic ligament in which the vagus nerve was

supposed to run. Now, as a matter of fact, only in a very few cases does the so-called anterior vagus nerve, containing fibres of the right and left vagus, run in the gastro-hepatic omentum. In most instances, it runs from the cardiac opening in the diaphragm right down on the anterior surface of the body of the stomach.

You may ask why divide the anterior vagus. Because, I am convinced that the posterior vagus has nothing to do with the HCl acid secretion. The posterior vagus is distributed to the pyloric end of the stomach, the duodenum and head of the pancreas and possibly is concerned in many of the pathological states of these organs. The anterior vagus emerges through the cardiac opening in the diaphragm in two or three distinct cords which can be easily palpated and just as easily divided and the results of division in high free HCl acidity are exceedingly promising in effecting an anacidity.

Dr. Babkin has stated that the volume of free HCl is probably diminished by vagotomy. We do not claim that the percentage of free HCl in the gastric secretion, namely 0.4% at the mouth of the tubules, is changed by vagotomy, but that the amount or volume of free HCl is markedly diminished, and that it is much easier for the regurgitant bile and pancreatic juice and mucus to neutralize a small volume of free HCl of .4% concentration, than a large amount of free HCl, of .4% concentration. That was the mistake of Dr. Benj. Berg's experiments. He estimated only the percentage of free HCl and not the volume.

I am sorry that my remarks offended Dr. Palmer and Dr. Andresen. I certainly didn't mean that they should and I simply asked for a closer cooperation so that the surgeon should not be asked to operate on cases in their final stage.

DR. CHESTER M. JONES (Boston): I should like to make one remark in relation to Dr. Winkelstein's question. He pointed out that his thirty cases did not develop anemia after the operation. I am sure that the answer is that his patients were on an adequate diet after operation and therefore in no danger of anemia. This, I believe, is the important point of the entire problem.

DR. RUDOLF SCHINDLER (Chicago) (closing the discussion): It is possible, Dr. Winkelstein, that you are quite correct. It may be that the anacidity in the post-operative stomach is due to a purulent post-operative gastritis which later turns slowly into atrophy.

But is it really desirable to replace one serious disease by another disease with a very doubtful prognosis? You may be right, that this might be of benefit to the patient, but perhaps often it is not. Furthermore, is it really necessary to produce anacidity, and if it is, is surgery necessary to produce it?

Dr. Palmer and his associates have shown that we can reduce the acidity by X-ray therapy, and that would probably be a safer procedure than resection. However, I am not convinced that the best results are obtained when anacidity occurs after gastric surgery. The few patients with a normal gastric mucosa and normal acidity, in whom the artificial stoma contracted rhythmically, showed a very beautiful result of gastric resection.

# Inhibition of Gastric Secretion in Man With Urogastrone\*

By

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and

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THE general use of a high fat diet in the management of peptic ulcer is based upon the observation that gastric secretion and motility are inhibited by neutral fat (1). The mechanism by which fat inhibits these activities was not understood until it was found that orally administered fat inhibited the motility and secretion of an auto-transplanted pouch of the stomach (2). It was then found that an extract of intestinal mucosa could be prepared, which on parenteral injection would inhibit gastric secretion and motility (3). The active principle was called *enterogastrone* (3). Enterogastrone has been concentrated and reliable methods for its assay have been developed (4), but it has not been sufficiently concentrated to warrant its use in man.

More recently attention has been directed to the urine as a possible source of the gastric inhibitory principle or principles. Sandweiss, Saltstein and Farberman (5) reported that commercial extracts of human pregnancy urine containing the chorionic gonadotropic hormone were potent in preventing or delaying the onset of experimental ulcers in dogs. Necheles (6) announced the presence of a gastric inhibitory substance in human urine. This announcement was confirmed for human pregnancy urine and for normal female and male urine (7). In addition an inhibitory factor has been reported to be present in the urine of patients with peptic ulcer (6, 7), pernicious anemia and gastric carcinoma (8), in the urine of normal dogs (9) and dogs subjected to gastrectomy or duodenectomy (10) and in the gastric juice of patients with pernicious anemia or gastric carcinoma (11).

The question of specificity arose when it was found that urine extracts contain a pyrogen, or fever-producing substance because fever depresses gastric secretion (12). However, extracts were prepared from human urine which were entirely free of pyrogenic impurity (13). When it was found that the gastric inhibitory factor was distinct from pyrogen, the gonadotropic hormones (7) and apparently the ulcer preventive factor of Sandweiss et al (14), it was given the name *urogastrone* (13). This term was coined to distinguish the urinary factor from enterogastrone, until the two had been proved to be identical.

In regard to the source of urogastrone, Culmer et al (15) found that when the small intestine of dogs is removed urogastrone disappears from the urine. It has been found recently that a control operation consisting of identical procedures with the exception that the small intestine was not removed from the abdominal cavity does not cause urogastrone to disappear

from the urine. These observations suggest that urogastrone comes from the small intestine.

Obviously, urogastrone, as well as enterogastrone, has therapeutic promise in that it may provide a practical method for the control of gastric secretion. With this idea in mind the effects of a purified preparation of urogastrone on gastric secretion in a group of human subjects have been investigated.

## METHODS

Two extracts of normal male urine which had been purified to different degrees were administered to the human subjects. Preparation A was obtained by the acid acetone fractionation method, which has been described elsewhere (16). Preparation B was obtained by a further purification which consisted essentially in dissolving the active fraction in 80 per cent acetone (made N/50 with HCl), removing the acetone, precipitating the active material with phosphomolybdic acid, and recovering the product as the chloride salt by washing with acidified acetone. Product B was at least twice as potent as product A, according to assays carried out on the dog.

The following procedure was used to measure the inhibitory effect of the extracts on gastric secretion in man. Nine healthy subjects swallowed a Rehfuß tube after a 14 hour fast and the stomach was completely emptied. For the next three hours the gastric contents were drained continuously in order to collect the entire secretions of the stomach. The subjects were not permitted to swallow saliva during this period. Samples were separated at ten minute intervals, their volume was recorded, and free acidity was determined by titration, using Topfer's reagent as indicator. During the first 20 minutes the control, or basal, secretion was collected. Following this histamine dihydrochloride was injected subcutaneously and the secretory response was obtained for the ensuing hour. At the end of this period, urogastrone was injected subcutaneously, 25 to 35 mgms. in the case of product A, 15 to 20 mgms. in the case of product B. One-half hour later the original dose of histamine was again injected subcutaneously and the secretory response was again obtained during the ensuing hour. The secretory response to the second dose of histamine, as compared to that of the first, constituted a measure of the inhibitory effect of the urogastrone. That the responses to two successive injections of histamine will ordinarily be quantitatively alike is well established by work reported in the literature and by our own observations. Hundreds of double histamine injections have been made in dogs, and although variations do exist, averages indicate, if anything, a slightly greater response to the second injection than to the first. Rivers and Vanzant (17)

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TABLE I  
*Response to histamine before and after urogastrone*

Subject	Mgm. Histamine	Mgm. Urogastrone	Before			After			Per Cent Reduction		
			Vol. cc.	HCl Mgm.	Max. HCl Cl. U.	Vol. cc.	HCl Mgm.	Max. HCl Cl. U.	Vol. cc.	HCl Mgm.	Max. HCl Cl. U.
1	0.1	30-35 A	135.0	342.0	170.9	67.5	195.0	113.2	50	49	17
2	1.0	30-35 A	28.3	6.4	6.2	10.2	0.0	0.0	73	100	100
3	0.3	30-35 A	79.3	229.9	127.5	76.2	177.4	161.7	4	51	20
4	0.3	30-35 A	120.6	211.7	79.0	28.5	41	12.5	76	98	84
5	0.5	25-29 A	89.0	155.6	54.7	48.5	61.8	55.0	45	58	6
6	0.3	15-20 B	77.5	215.3	97.2	47.0	76.5	55.5	39	64	78
7	0.3	15-20 B	100.5	327.4	114.5	27.5	69.3	59.2	72	82	22
8	0.3	15-20 B	95.5	298.7	106.7	65.0	119.1	83.8	29	60	22
9	0.3	15-20 B	107.5	224.5	89.7	95.0	141.4	77.5	10	37	8
Average			94.7	238.4	88.9	51.6	84.9	65.5	45	67	31

have demonstrated the same in 66 human subjects, and in the course of other work in progress in this laboratory these results have been confirmed on human subjects.

### RESULTS AND DISCUSSION

In Fig. 1 the results are presented in the form of a graph which represents the average of the group of nine subjects. The graph shows the average volume, the average acidity, and the average quantity of acid for each of the 10 minute periods during the entire experiment. It is evident, first, that the response to histamine is less after the administration of urogastrone, and, second, that during the half-hour period immediately following the injection of urogastrone the basal secretion fell significantly below the level exhibited during the first 20 minutes of the experiment.

In Table I the responses to histamine before and after the administration of urogastrone are shown for each of the subjects. It can be seen that each subject exhibited a reduction in the volume, the acidity, and the acid output following the injection of urogastrone.

The percentage reduction in the volume of gastric juice varied from 1 per cent to 75 per cent for the different individuals, with an average of 45 per cent. The free acid output was reduced somewhat more, averaging 67 per cent with a range of from 37 per cent to 100 per cent. The maximum free acidity was also reduced with a range of from 4 per cent to 100 per cent and an average of 31 per cent. When one calculates the average acidity (not shown in the table) of the entire one hour response to histamine considered as a single pooled sample, the range of inhibition is from 0 to 100 per cent, with an average of 44 per cent. It should be pointed out that the 100 per cent inhibition in the above examples occurred in subject No. 2, whose response to one mgm. of histamine was so small as to render the results obtained with him of little value.

The basal secretion of gastric juice was also reduced by urogastrone. A comparison of the twenty minute periods which immediately preceded the two injections of histamine reveals that the volume,

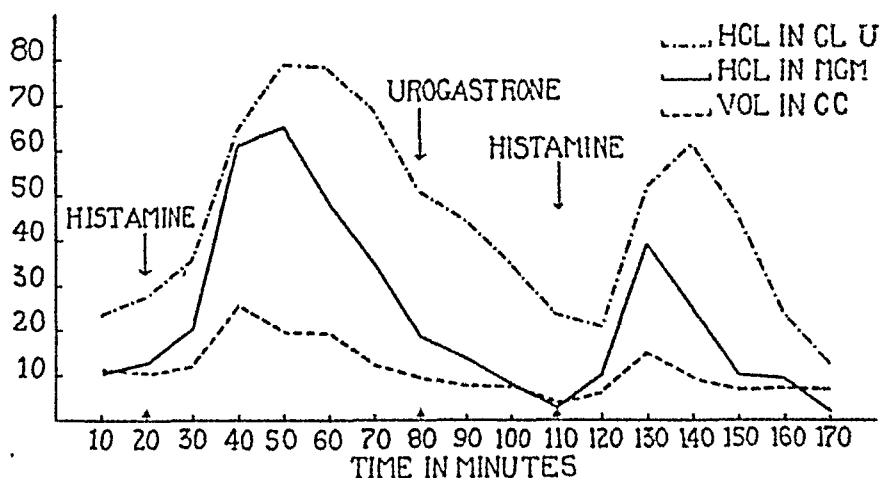


Fig. 1. Average curve from nine experiments showing the response to histamine before and after the injection of urogastrone.

acidity, and acid output were reduced on the average of 43, 0 and 38 per cent respectively.

The administration of these comparatively large doses of urine extracts were accompanied by very little side action. No rise in oral temperature occurred, nor were there any systemic reactions, unless they could have been so mild as to be obscured in some of the subjects by the headache and lassitude which they ordinarily experience after repeated injections of histamine. Locally at the site of injection each subject noted from 8 to 20 hours later an area of erythema approximately 4 to 6 cm. in diameter. Those subjects who had received the less pure product, A, noted local tenderness and possibly edema, but those who had received the more potent preparations, B, experienced only very mild tenderness and no appreciable edema. None of the subjects suffered any aches or pains in adjacent muscles or joints.

In our opinion the preparation of urogastrone used in these experiments is not sufficiently concentrated

or "purified" to warrant its clinical use. It is very probable, however, that the impurity which is responsible for the local hyperemia can be removed. In fact, since these experiments were performed, considerable purification of the extracts has been accomplished. A product free of irritating properties and allergins would deserve clinical trial. If it proved to be useful, the supply would be limited, however, until the active principle is synthesized.

## SUMMARY

The subcutaneous administration of a potent preparation of urogastrone to nine human subjects significantly reduced the gastric secretory response to histamine with regard to the volume of gastric juice, its acidity, and the output of free acid. This inhibitory action was obtained with no other observed effects than a mild local erythema and tenderness at the site of injection.

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## Pectin Therapy and Pectin Types

By

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### A. Introductory Remarks

SINCE 1935, considerable research has been carried on in this country on the use of pectin in intestinal and peptic dysfunctions and in the treatment of wounds, burns and the like. "Pectin" is an all-inclusive designation for a group of substances usually characterized by the property of forming jellies with

certain precipitants. Pectins differ greatly, hence it is essential that in each investigation the identity and properties of the pectin used be known with certainty.

It is the purpose of this paper to give the doctor, and those engaged in clinical research, definite information concerning the physical and chemical properties of pectins which may serve as a basis for their proper and intelligent use and evaluation. It is the author's hope that, as a result, more research will be

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stimulated in this field which appears of particular promise to the industrial surgeon and to the military surgeon concerned with the treatment of war wounds. It is noteworthy that the Regional Research Laboratories, U. S. Department of Agriculture, have included pectin among prospective fields of research, defining the problem in these words (1):

"The therapeutic use of apple concentrate to furnish galacturonic acid as a precursor of mucin in the treatment of ulcers, toxemia of pregnancy, and other intestinal disorders. This field has just been touched upon and deserves further consideration."

#### B. Brief Review of the Therapeutic Position of Pectin

Therapeutic uses of pectic substances are not new. Braconnot, the French physician who discovered and named pectic acid in 1825, observed its reactions with heavy metals and suggested its use as an antidote for heavy metal poisoning (6). This is particularly interesting in view of a recent paper by Shields, Mitchell and Ruth who show that apples contain a substance, presumably pectin, which prevents the assimilation of lead added in the form of lead arsenate spray (16).

1. *Pectin Therapy in Gastro-Intestinal Disorders.* Pectin therapy for diarrheal disorders has been a natural outgrowth of the well known apple therapy and inasmuch as the older literature has been repeatedly reviewed (see for example J. A. M. A., 109:1636, 1937) reference need only be made to the recent conclusive data of Winters et al (20) and Manville et al (14). Both groups have presented extensive clinical data. The use of pectin in connection with gastric ulcers (21) appears as a logical extension of its use with diarrhea and dysentery, but as yet has not been subjected to such extensive clinical tests.

2. *Pectin as a Hemostatic.* The origin of the use of pectin to accelerate blood clotting is rather obscure. Apparently Violle and Saint-Rat (19) first described this use in 1925. However, in their early work they used injections of pectin solutions followed by pectase and reported that the animal, in about 10 minutes, passed into convulsions, coma and death. Subsequent workers using pectin only have reported definitely increased velocity of blood coagulation (10, 13) and claim it to be "absolutely harmless."

The action of pectase is that of demethoxylation. One may, therefore, assume that in the Violle and Saint-Rat experiments the pectin became demethoxylated after which it reacted with the calcium in the blood to form clots of insoluble calcium pectate. This suggests that for this type of work a pectin of high methoxyl content, not precipitable by calcium, should be used. The physician must keep in mind that while one type of pectin may be absolutely safe another type may be dangerous for intravenous injections.

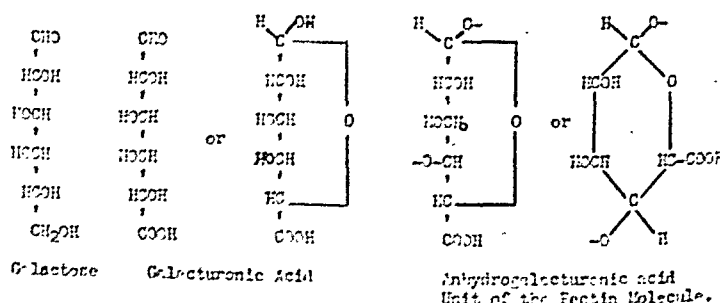
3. *Pectin as a Surgical Dressing.* The more recent use of pectin therapy for surgical dressings, particularly in cases of infected wounds and burns appears to have come about as an outgrowth of gastro-intestinal therapy and was stimulated by the observation that pectin solutions had a bactericidal effect. Haynes, Tompkins, Washburn and Winters (12) reported "very satisfactory results" when aqueous solutions of pectin were used in the treatment of wounds including osteomyelitis and other deep wounds, as well as superficial wounds which had not responded well to ac-

cepted methods of treatment. The Journal of the A. M. A. (2) in commenting on the work of Haynes et al, suggested the further study of pectin as a surgical dressing. The work of Thomson (18) and many other yet unpublished cases, establish the merit of 2% pectin solutions in the treatment of infected wounds, but other work has proven the fallacy of the bactericidal theory as an explanation for such action (12a). Pectin as such is not bactericidal, yet as Thomson pointed out, the healing time of infected soft tissue wounds, pressure sores, ulcers, osteomyelitis, compound fractures and the like is markedly reduced by the proper administration of pectin solutions as a dressing. With these facts in mind it requires little imagination to visualize the important possibilities of pectin therapy in connection with the surgical problems confronting nations at war.

Unpublished results indicate beneficial effect from the local application of pectin in the case of desquamatory gingivitis and similar dental conditions, and very recently Fantus and Dyniewicz (8) have reported "phenomenal results from the paste treatment of bed sores." Two pectin pastes and some gum tragacanth pastes were used by them. The fact that both were effective naturally brings to mind the close relationship between those two products. The uronic acid content of gum tragacanth is over 30%, and while no analyses were given the uronic acid content of the diluted (100 Grade) pectin used would be of approximately the same order. It is possible therefore that, entirely aside from the natural hydrophilic properties involved, the therapeutic effect in either case may be fundamentally the same. However, pectin has the advantage that its chemical composition has been subjected to more complete study.

4. *Theory of Pectin Therapy.* No well substantiated theory of the mechanism underlying pectin therapy has been brought out, however, Bittner (4) and others have suggested that the action is entirely one of absorption of the toxic effect of bacterial invasion. The pectin removes the exotoxic products of bacterial growth thereby relieving the system from the absorption of these products and allowing the bloodstream defenses to concentrate on the bacterial invasion. This viewpoint helps explain not only the pectin therapy in the case of gastro-intestinal disorders but also its effectiveness in the treatment of external infected wounds. Manville also pointed out that the galacturonic acid present in pectin is as capable of forming conjugation products with toxins, as is glucuronic acid, and therefore has a mucin sparing effect. Ziegelmayr, using frogs as experimental animals, concluded that pectin is an adsorption agent for different toxins (22).

Galacturonic acid is related to galactose in the same manner as glucuronic acid is related to glucose. The following formulas show these relationships and also



illustrate two different methods of indicating the pyranose configuration of the galacturonic acid anhydride units present in the pectin molecule.

The significance of glucuronic acid in the economy of the organism has been repeatedly emphasized. The part it plays in detoxication in the body has been the subject of considerable research. Other naturally occurring uronic acids, such as the galacturonic acid from pectin, apparently have the same property of conjugating with toxic substances and thereby aid in the elimination of the latter. This supplies the only rational explanation which has been put forward to explain the mechanism involved in pectin therapy.

### C. *The Chemistry of Pectin*

Even a very brief review of therapeutic uses of pectin suggests that the physician using pectin should have available exact information about the chemistry of the pectin molecule, and more specifically he must know in some detail the special properties of any particular commercial pectin preparation used. Different pectins may have entirely different compatibilities.

Pectins may be extracted from a variety of plant materials. Apples, beets and the peel from citrus fruits are particularly rich in pectin, which is obtainable by controlled acid extraction. To obtain the pectin in dry form the clarified extract is precipitated either by alcohol or by salts of certain metals such as aluminum, copper and calcium. Alcohol precipitates appreciable amounts of araban and galactan along with the pectin, and their complete separation from pectin is very difficult. The extraction procedures may be varied so as to obtain pectins with more or less free acid groups; that is, the pectins may be demethoxylated to suit requirements for different purposes.

During the 100 year interim period from Braconnot to the rediscovery of pectin therapy, this substance continued to fascinate chemists. The chemistry of pectin has, therefore, been the subject of extensive research, but the complex colloidal nature of the substance permitted only slow progress. The many erroneous conceptions which have been in vogue at one time or another need not be discussed here. The modern viewpoint really started with von Fellenberg (9) and Ehrlich (7) about 1915. The former proved that the pectin molecule contained several acid groups, some of which were neutralized by methyl alcohol in ester linkage. Shortly afterwards Ehrlich proved that the organic acid present in pectin is galacturonic acid. Ehrlich has been a prolific writer, but unfortunately, his nomenclature and a large portion of his work has served chiefly to obscure the rational approach to pectin chemistry, especially since it has found its way into nearly all the currently available "Handbuchen" on the subject.

The present conception that pectin is a chain molecule made up of partially methylated galacturonic acid anhydride units greatly simplifies the interpretation of pectin properties (5, 11). Acid properties are conferred by the free carboxyl groups resulting from partial demethoxylation. The reactions of pectin (preferably called pectinic acid) are essentially those of a typical organic acid of high molecular weight. The colloidal properties are indicative of the number of units in the chain. The main difference between pectic acid and pectinic acid is that the former is more completely demethoxylated than the latter. That is, it has more free acid groups, a lower equivalent weight, as

determined by simple titration. Both pectins and pectic acid of greatly varying molecular size, as indicated by specific viscosity and gel properties, do exist; but usually pectic acid will be found to be of considerably lower molecular weight, as indicated by specific viscosity, than is normal for pectin.

A high grade pectin may have a molecular weight of over 200,000 (17). This means that well over 1000 galacturonic acid units may be strung together to form each molecule, which accounts for the viscous nature of pectin solutions. Improper methods of preparation may result in such molecules being split into shorter fragments of corresponding lower molecular weight, lower grade, and lower viscosity, yet of essentially identical chemical composition.

The more free acid groups, the more reactive the pectin is towards metal salts. This change in acidity is independent of molecular weight and of jelly grade. However, completely demethoxylated pectin is the so-called *pectic acid*, which is not suitable for the preparation of fruit jellies. The equivalent weight—that is, the weight of pectin per free acid group—may range from about 1000 down to about 200 for pectic acid.

Usually pectins as obtained from various plant materials are accompanied by appreciable amounts of other affiliated compounds. It is a debatable question whether some of these may be in loose chemical combinations with the pectins. Two polysaccharides, the pentosan araban and the hexosan galactan, are common constituents of some pectin preparations and may introduce errors in the equivalent weight determinations simply because they act as inert diluents. For this reason equivalent weight and methoxyl determinations on alcohol precipitated pectins may not be properly descriptive of the true pectin fraction. By metal precipitation a purer pectin can be obtained.

The reactions of pectin and pectic acid with certain metal ions to form insoluble compounds have long been known. Such insoluble precipitates have been described by a number of writers from Braconnot to von Fellenberg. From a study of several pectins differing in methoxyl content von Fellenberg correctly concluded that "the more methoxyl groups are split off the more acid groups are present in the pectin molecule and the easier does coagulation with metal salts occur."

Naturally one may expect pectic acid to form insoluble precipitates with many salts which do not precipitate pectins of high equivalent weight because the latter do not combine with enough of the precipitating ion to become insoluble. For example ordinary high combining weight pectin reacts with small amounts of calcium to form calcium pectinate but it does not form a precipitate with calcium, whereas the insoluble calcium pectate provides the well known method for determining pectic acid. Likewise, pectins of about 475 equivalent weight or less are readily precipitable by calcium (15). Other metallic ions may form precipitates with pectins of higher equivalent weight, for example aluminum, copper, iron, nickel and others. This, of course, is what might be inferred from von Fellenberg's general statement quoted above. The maximum equivalent weight at or below which precipitation may occur varies to some extent with different metallic ions; and inasmuch as such precipitates tend to be soluble in acids, the maximum equivalent weight

at which precipitation occurs will also vary with the pH of the solution. The higher the pH the easier is the precipitation.

The alkali metals and ammonia also react with pectin in stoichiometric proportions but form only soluble salts.

Cations are readily removed from powdered pectin by washing with acidified alcohol and the excess acid can be removed by washing with plain dilute alcohol. Such washed pectins in 1% solution will have a pH well below 3.0, and should preferably be referred to as pectinic acids.

Pectin is, of course, sold largely for its jelly properties. It is, therefore, evaluated on the basis of the amount of jelly which one pound of pectin will produce. "Grade" when used in connection with pectin means *strength* and 100 Grade means that 1 pound of the pectin can be used along with 100 pounds of sugar and the necessary water and acid to produce standard strength jelly. Similarly a 300 Grade pectin will carry 300 pounds of sugar for each pound of pectin.

The physician is interested in grade for two reasons. First, he must pay on the basis of grade, because the market price is based directly on the grade. Second, particular care in the manufacturing process and the subsequent purification is required in order to produce pectins of high strength, therefore, the specification of high grade pectin is also the best assurance that the pectin is of high quality and purity.

The physician may well become confused by trade designations of "rapid set" and "slow set." These terms have no meaning in connection with therapeutic pectins, but the degree of methylation or rather the proportion of free acid groups expressed in terms of equivalent weight is important because it controls the acidity of the pectin and its reaction towards metallic ions. The reactivity towards calcium is of particular significance in connection with pectins used intravenously or in the spinal canal.

The following table presents the properties of most interest for three types of apple pectin in current commercial production and currently used for different therapeutic purposes.

The most essential data for the physician to keep in mind in a selection of a pectin or pectins for clinical use may be summarized as follows:

1. *Source.* Pectins are obtained by controlled acid hydrolysis of vegetable tissues. Chief commercial sources in this country are apples and citrus fruits.

2. *Molecular Structure.* The pectin molecule is composed largely of chains of anhydro galacturonic acid units some of which are methylated. The molecule may contain over 1000 uronic acid units, that is a molecular weight of about 175,000-250,000 is assumed for high grade pectin. The colloidal properties are functions of the high molecular weight. Commercial "Grade" is indicative of the molecular weight.

3. *Equivalent Weight.* Pectins are organic acids, reacting with either organic or inorganic bases in stoichiometric proportions. The number of free acid groups depends on the degree of methylation. Equivalent weight is a measure of the acidity and reactivity, it varies independently of "Grade." Pectins of equivalent weight from about 1000, down to about 200 for pectic acid can be prepared commercially. The natural pH of ash-free commercial pectins in 1% solution would be in the range of pH 2.5-2.8, but usually the free acidity is partially neutralized to give more stable products with pH well above 3.0. Sodium or calcium are commonly used for this purpose.

4. *Solubility.* Pectins are soluble in either water, saline solutions, or dilute acid, but not in dilute alcohol. (Dilute alkalis cause demethoxylation). Most pectins gum and ball up when added to water, requiring a long time of soaking to obtain complete dispersion and solution. Such pectins go into solution without lumping if first dispersed in alcohol, glycerine or heavy sugar syrup. Dispersible quickly soluble powdered pectins are, however, obtainable.

A 5 Grade solution is convenient for most purposes; that is, about 5% of 100 Grade or 2% of 250 Grade pectin. Any considerably greater percentage is difficult to handle because of the high viscosity.

5. *Reactions with Metal Ions.* The reactions of pectins with metal ions differ with the extent of demethoxylation. The more methoxyl groups are split

*A comparison of the properties of certain commercial pectins of different equivalent weights*

Type Number	Aver. Eq. Wt.	Approx. Methoxyl Content %	Amt. of Metal Ion if Completely Neutralized			Precipitation With Metallic Ions				pH of 1% Pectin Solu.		Approx. Normal Grade of Pectin	Remarks
			Na %	Ca %	Al %	Cu	Al	Fe	Na	Washed Ash-free	Commercial Neutralized		
1*	920	11.2	2.5	2.2	1.0	No	Yes	Yes	No	2.75	3.0-3.5	270	Suitable for use in presence of calcium. Will carry small amount of Fe and other ions, without precipitation.
2	570	9.1	3.9	3.4	1.5	No	Yes	Yes	No	2.7	3.0-3.8	285	Addition of calcium increases viscosity of pectin solution.
3	420	7.3	5.2	4.6	2.1	Yes	Yes	Yes	No	2.6	3.0-3.5	300	Addition of small amounts of calcium cause tremendous increase in viscosity of pectin solution.
4**	200	<0.5	10.3	9.1	4.3	Yes	Yes	Yes	No	2.55+	3.0-3.5	None	Soluble as sodium or ammonium salt. Small amounts of calcium cause gel formation.

\*"Certo" is the trade-mark of General Foods Corporation for its pasteurized acidulated apple pectin solution. The pectin contained therein is of this B No. 1 type and the amount is approximately the equivalent of 2% 250 Grade pectin. Certo contains additional small amounts of carbohydrate material, 0.5% ash and edible lactic acid to give a pH of about 3.0. The pure pectin in powdered form is known as Certo B No. 1.

\*\*Pectic Acid, included for comparison.

+Suspension of powdered pectic acid.

off the more free acid groups there are present in the pectin molecule and the more readily the pectin reacts with the alkaline earths such as calcium to form insoluble compounds. The alkali metals (K, Na, NH<sub>4</sub>) form only soluble salts, but Al, Cu, Fe, Ni and other heavy metal ions react even with high equivalent weight pectin to form insoluble precipitates.

Commercial pectins may be markedly affected in their properties by either accidental or deliberate addition of metal ions, such as for example nickel or aluminum.

6. *Purification Methods.* Powdered pectins and insoluble metal precipitates of pectin can be washed with either 50% alcohol or acidified 50% alcohol to remove sugars, glycerine, ash constituents and other impurities which are commonly present in commercial pectin preparations. The washed powder can be readily dried by use of either strong alcohol, acetone or ether.

7. *Viscosity of Pectin Solutions.* The lower the equivalent weight the more the viscosity is subject to change due to change in pH or in salt content. Pectins

of high combining weight are but little affected by changes in the pH; and such metallic ions as have a precipitating effect cause in lower concentrations an increase in viscosity. High molecular weight is reflected in high specific viscosity and high commercial grade.

8. *Stability.* Ash free pectins are not very stable and should preferably be kept in a refrigerator, but pectins adjusted with either sodium or calcium to pH 3.0-3.5 are quite stable and are preferable for most purposes.

## CONCLUSION

Commercial pectins are commonly adjusted as to "Grade" by dilution with cerelese, glycerine, etc. The physician should know whether his preparation is all pectin, the grade of the pectin, and what diluents are present. In addition he needs to know ash content and the chief ash constituents, as well as the combining weight. With this knowledge pectin therapy will become more of an exact science.

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# Woldman's Phenolphthalein Test in Intestinal Tuberculosis

By

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THE difficulty of establishing a diagnosis of intestinal tuberculosis by clinical and roentgenographic methods has been the subject of many reports (1, 2, 3, 4). When Woldman's preliminary paper (5) on the use of phenolphthalein as an indicator of gastro-intestinal ulceration appeared, we began a study of a group of patients with active pulmonary tuberculosis, hoping that with the test we might make the diagnosis of ulceration during life.

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According to Woldman, the presence of free phenolphthalein in the urine, two, four or six hours after ingestion of 0.1 gm. of the drug indicates a break in the mucous membrane of the gastro-intestinal tract. Its absence from the urine after these intervals indicates an unbroken mucosa.

## CLINICAL STUDY

Two hundred seventy-one tests were performed on 206 patients. Forty-three had two tests and 11 had three tests. There were 173 active tuberculous patients, the majority with progressive pulmonary

TABLE I  
*Results of the phenolphthalein test in non-tuberculous patients*  
33 patients

Without Clinical or Autopsy Evidence of Gastro-Intestinal Ulceration. 28 Cases			With Clinical or Autopsy Evidence of Gastro-Intestinal Ulceration. 5 Cases		
Diagnosis	Positive P.P. Test	Negative P.P. Test	Diagnosis	Positive P.P. Test	Negative P.P. Test
Cardiac cases—10 (Autopsy—1)	3	7	Ulcerative colitis—4	3	1
Neurologic cases—17 (Autopsy—1)	13	4	Lymphosarcoma with stomach ulceration—1 (Autopsy—1)		1
Hodgkin's disease—1 (Autopsy—1)		1			
Total	16	12		3	2

lesions. In addition, 33 non-tuberculous patients were tested.

Table I records the results of the test in the 33 non-tuberculous patients. Four patients in this group came to autopsy.

One sees that a positive test resulted in 16 of 28 patients in whom there was no expectation, on clinical grounds, of gastro-intestinal ulceration. On the other hand, in two of five patients with unequivocal evidence of gastro-intestinal ulceration, the test was negative. In similar series of control patients, LeVine and Kirsner (6), Notkin, Kirsch and Albert (7) and Steigman and Dyniewicz (8) reported a total of 172 positive tests in 307 patients (56%).

When we carried out the test on 173 patients with pulmonary tuberculosis and its complications, 92 (53%) gave a negative result. Eighty-one (47%) of this group gave a positive test, a result not significantly different from the 56 per cent positive finding, cited above, in a large group of patients with no known or suspected disease of the gastro-intestinal tract.

#### AUTOPSY CORRELATION

Post-mortem examination was performed on 33 patients. Twenty-nine of these died of progressive pulmonary tuberculosis and its complications. The findings are tabulated in Table II.

Five of the 12 patients with post-mortem evidence of a normal bowel tract gave positive phenolphthalein tests, i.e. a positive error (a positive test encountered where there is no ulceration) of approximately 42 per cent. Four of 21 patients with post-mortem evidence of ulceration exhibited negative tests, i.e. a negative error (a negative test encountered where there is ulceration) of approximately 19 per cent.

The 42 per cent positive error approximates the figures reported by LeVine and Kirsner (6) and Notkin, etc. (7). Their negative error was higher than our 19 per cent, being respectively 38 per cent and 30 per cent. The reason the negative error is smaller in a series of patients who come to post-mortem examination with a high percentage of intestinal ulceration becomes apparent on further examination of Table II.

It is to be noted that 21 out of 33 showed an ulcerative lesion of the gastro-intestinal tract at autopsy. Our series, therefore, differs from other clinical series reported where the incidence of suspected or proved ulceration was low. The parallelism between the test and autopsy findings occurred predominantly in cases showing ulceration of the bowel tract, i.e. in 17 of 21 instances. When no ulceration was present at autopsy, the test was wrong in almost half the cases, 5 out of 12.

Recalling the fact, cited above, that 56 per cent of

TABLE II  
*Correlation of autopsy with the results of the phenolphthalein test—33 autopsies*

With Ulceration of the Gastro-Intestinal Tract. 21 Cases			Without Ulceration of the Gastro-Intestinal Tract. 12 Cases		
Diagnosis	Positive P.P. Test	Negative P.P. Test	Diagnosis	Positive P.P. Test	Negative P.P. Test
Pulm. tbc. with tbc. enteritis	17	3	Pulm. tbc. with normal G.I. tract	3	6
Lymphosarcoma of stomach with ulceration		1	Hypertension with cardiac failure	1	
			Encephalomyeloradiculitis, Bilateral bronchopn.	1	
			Hodgkin's disease		1
Total	17	4		5	7

307 patients in whom no clinical or roentgenographic evidence of gastro-intestinal ulceration existed gave false positive reactions, one can then understand that the coincidental agreement between the test and clinical and autopsy findings will rise, *pari passu*, with the increasing incidence of ulceration in the series. Conversely, the less frequent the incidence of ulceration in the series, the more clearly do the false positive reactions stand out, and the more obvious becomes the unreliability of the test.

Others (6, 7, 8, 9) have shown that the phenolphthalein test is unreliable in the diagnosis of peptic ulcer. Our findings, supported by post-mortem control of the test hitherto lacking in other series, indicate that the test is also unreliable in the detection of gastro-intestinal tuberculosis.

### SUMMARY

1. 271 phenolphthalein tests (Woldman) were performed on 206 patients in order to determine the value of the procedure in detecting the presence of ulceration of the gastro-intestinal tract.

2. 173 patients with active pulmonary tuberculosis and 33 non-tuberculous patients were studied. 33 of the series had post-mortem examinations.

3. Autopsy controlled cases revealed that the test had a "positive" error of 42 per cent and a "negative" error of 19 per cent.

4. The Woldman phenolphthalein test is of no value in determining the presence or absence of tuberculous ulcers in the gastro-intestinal tract.

We wish to express our gratitude to Miss Florence Friedman, technician, Division of Pulmonary Diseases, for her valuable assistance.

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## Vitamin K Deficiency in a Case of Gall Bladder Disease Without Clinical Jaundice or Hepatitis†

By

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**A** CASE of gall bladder disease recently observed on the surgical wards of Stanford University Hospital is worthy of note for the following reasons. *First*: the patient showed a prolonged plasma coagulation time (modified Howell prothrombin time) indicative of Vitamin K deficiency without presenting any of the usually recognized causes of such a deficiency. *Second*: the intramuscular injection of 4-amino-2-methylnaphthol hydrochloride (Vitamin K-5)\* reduced the plasma coagulation time to normal within a period of less than 24 hours, eliminating the risk of post-operative hemorrhage. *Third*: repeated blood studies strongly suggested that Vitamin K therapy by mouth might not have been effective in this case.

### CASE REPORT

Mr. C. W., a 55-year-old married white miner entered the hospital January 8, 1940, complaining of right upper abdominal pains for the past nine months. These had occurred weekly in attacks lasting some twelve hours. The pain radiated to the back and soreness persisted under the right rib margin for at least a day after the pain had left. He had had slight nausea with these attacks but no vomiting. Two weeks before he entered the hospital the pain had become constant; he noted that his stools were light colored, his urine dark, and jaundice appeared. Four days before entry the pain had again left and his jaundice had faded. His past history was not remarkable except that he had had typhoid fever 40 years before. He had

suffered from hay fever and sour stomach on and off for years. Although he had drunk alcoholic beverages in the past, he had abstained from them for several years. Physical examination was essentially negative except for a questionable icteric tint to the skin and sclerae, abdominal tenderness at the right costal margin, and a palpable liver edge, which was slightly tender.

The laboratory examination revealed a normal blood count. The blood Wassermann was negative. The urine was positive for bile pigments but otherwise was not remarkable. His stools were normally pigmented. The icteric index was 14 units on January 9 and 15 units on January 10. The blood coagulation time was 8 minutes and his plasma coagulation time was 27 minutes, when recalcified with an optimum amount of calcium. With an excess of calcium (2½ times the optimum amount) the coagulation time was one hour and ten minutes. His bleeding time was 3 minutes. An electrocardiogram was normal. An X-ray gastro-intestinal series and barium enema revealed nothing unusual. The pre-operative diagnosis was common duct stone. Because of his prolonged plasma coagulation time, he was given injections of Vitamin K pre-operatively on January 10, 1940.

The relationship of this treatment to his blood findings is shown in Table I and graphically in Fig. 1. As the coagulation time was normal the next day, he was operated upon. A diseased gall bladder with thick, fibrous walls was found. It contained two stones. The common duct was not dilated but was opened and probed and no stones were found. A liver biopsy was taken which microscopically was reported as normal. The histological diag-

\*This product was supplied by the Parke Davis Company.

†From the Department of Medicine, Stanford University Medical School. Submitted May 11, 1940.

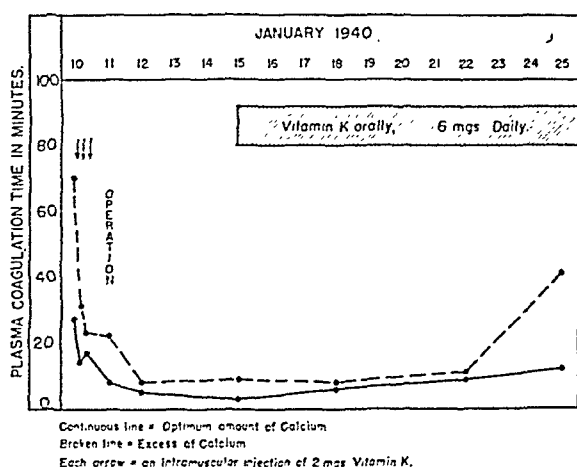


Fig. 1. The relationship of the plasma coagulation time to parenteral and oral Vitamin K therapy in a case of chronic cholecystitis.

nosis was cholecystitis, chronic, and cholangitis chronic, mild.

The patient had an uneventful post-operative course. Oral Vitamin K therapy was started post-operatively, as indicated in Table I and in Fig. 1, and continued until the patient was dismissed on January 25, two weeks after operation.

Why this patient should have a Vitamin K deficiency is not clear. The well-recognized causes of such a deficiency in an adult are: (1) a diet so deficient in fat that the fat soluble Vitamin K, whether exogenous or endogenous in origin, cannot be absorbed; (2) absence of bile in the intestinal tract due to blockage of the common bile duct, severe hepatitis or biliary fistula

so that fats cannot be absorbed; (3) disease of the bowel wall interfering with the normal processes of absorption such as might occur in sprue or in multiple intestinal strictures; and finally (4) disease of the liver which would interfere with assimilation of the vitamin. A diet totally deficient in Vitamin K, or excessive diarrhea causing elimination too rapidly to permit absorption, are also possible causes of Vitamin K deficiency. This patient was on an adequate diet, had bile in his intestinal tract, showed no evidence of intestinal disease, and his liver was normal, grossly and microscopically. Some further explanation of the prolonged plasma coagulation time must be found.

Plasma coagulation times of 27 minutes and 70 minutes represent a marked prolongation by this method. The normal average time based on a study of 100 normal subjects is 5.38 minutes, the limit of variation being between 2 and 8 minutes, when an optimum amount of calcium is used (1). When a known excess of calcium is used which tends to exaggerate the clotting defect, the average time is 8.61 minutes, the limits of variation being between 3 and 15 minutes. As this method has proven satisfactory in studying plasma coagulation time changes in 100 chicks with experimentally produced Vitamin K deficiency and in a number of patients, and as the response to therapy is so clear-cut in the case described, the prolonged plasma coagulation time may be taken as an indication of Vitamin K deficiency.

It is probable that the abnormal blood findings are dependent on a disturbance in biliary tract function which is not demonstrable in terms of a hepatitis. Three other cases have been studied in which prolonged plasma coagulation times were apparently due to cholecystitis, and in two these times returned to normal after acute attacks. Spontaneous hemorrhage

TABLE I

The relationship of Vitamin K therapy to blood and plasma coagulation estimations in a case of chronic cholecystitis

Date	Time	Vitamin K Therapy	P. C. T.* Optimum Calcification	P. C. T.* Excess Calcium	Blood Coagulation Time	Remarks
1940						
Jan.						
10th	10:30 a. m.	None	27 mins.	70 mins.	8 mins.	
10th	1:00 p. m.	2 mgs. i. m.**				
10th	2:30 p. m.		14 mins.	31 mins.	7 mins.	
10th	4:00 p. m.	2 mgs. i. m.				
10th	8:30 p. m.		16 mins.	23 mins.	5 mins.	
10th	9:00 p. m.	2 mgs. i. m.				
11th	9:15 a. m.		8 mins.	21 mins.	16 mins.	Operation
12th	9:50 a. m.		5 mins.	8 mins.	12 mins.	
15th	9:40 a. m.	6 mgs. orally	3 mins.	9 mins.	11 mins.	
18th	10:50 a. m.	6 mgs. orally	6 mins.	10 mins.		
22nd	12:45 a. m.	6 mgs. orally	9 mins.	11 mins.	5 mins.	
25th	9:55 a. m.	6 mgs. orally	12 mins.	41 mins.	12 mins.	Left hospital

\*Plasma coagulation time.

\*\*Intramuscularly.

did not occur in any of these cases, but it did occur in two of four cases reported by Pohle and Stewart (2). In two of their cases clinical jaundice was not present as their icteric indices are recorded as 2 and 12, and in the others it was only 20 and 60 units respectively. All but one of these cases showed a very low prothrombin level and in two serious bleeding occurred. The diagnosis was verified in each by either operative or autopsy findings. The authors make no comment as to the mechanism involved in producing Vitamin K deficiency in these patients with gall bladder disease.\*

If a patient with cholecystitis, with or without jaundice, may develop a disturbance in the blood clotting function which may in certain instances lead to excessive bleeding and this hemorrhagic tendency can be controlled by the administration of Vitamin K, then all patients with gall bladder disease should have tests of their plasma coagulation time or so-called "prothrombin time" before submitting them to operation, even though post-operative hemorrhage is a rare complication. The patient described might well have developed troublesome bleeding if the blood coagulation defect had not been determined and appropriate therapy carried out.

The rapid improvement in the plasma coagulation time in this patient after receiving three injections of 2 mgs. each of 4-amino-2-methyl-naphthol hydrochloride within a period of eight hours and the continued improvement during the next five days without further treatment have not been reported previously. However, Snell and Butt (3) in a supplementary report on Vitamin K in the Journal of the American Medical Association of December 2, 1939, discuss the development of this group of drugs with Vitamin K activity and mention two reports of its use parenterally.

In the case here reported the plasma coagulation time fell from 27 minutes to 14 minutes, one and one-half hours after the first injection which is in keeping with the rapid shortening of the blood coagulation time occurring in Vitamin K deficient chicks receiving intramuscular injections of Vitamin K (4). Twenty hours after the first injection and on the day of operation, the plasma coagulation time was 8 minutes with

a gradual descent to 3 minutes by the fourth post-operative day. These figures suggest that a single injection of 6 mgs. or more of the substance used might be sufficient to protect a patient through the whole critical period when bleeding might occur.

An inability to absorb Vitamin K from the intestinal contents due to a disturbed function of the intestinal mucosa or possibly some disorder of fat digestion interfering with the normal metabolism of this vitamin would make imperative the administration of Vitamin K parenterally instead of by the oral route. So far no instance of such a disorder has been clearly shown, and in most patients with Vitamin K deficiency feeding the vitamin by mouth has been highly satisfactory. However, the blood findings in the present case indicate that oral therapy was not effective. After the reduction of the coagulation time to normal following parenteral therapy, the time gradually increased again from the fifth post-operative day to the fourteenth, when the patient left the hospital and also the state. This rise is clearly shown in both the table and the chart and took place during daily oral Vitamin K therapy. It would seem to be significant as abnormal figures were gradually reached in both series of tubes, the one for the optimum amount of calcium being 12 minutes and the one with an excess of calcium 41 minutes the day of dismissal. The enforced termination of the studies at this time is most unfortunate.

#### SUMMARY

A patient with cholecystitis with a prolonged plasma coagulation time (modified Howell prothrombin time) indicative of Vitamin K deficiency was successfully treated with this vitamin parenterally; and subsequent therapy per os suggested this form of treatment would not have been satisfactory. None of the usual explanations for Vitamin K deficiency seemed tenable in this case of cholecystitis.

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\*H. P. Smith in his discussion of an article on Jaundice appearing in the *J. A. M. A.*, 113:2056, Dec. 2, 1939, states that he has observed cases of gall bladder disease complicated by serious hemorrhage.

## Giant Colon in an Adult Psychotic Patient With Necropsy Report\*

By

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and

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WE are herein reporting a megacolon which, as far as we have been able to ascertain, is the largest heretofore reported.

When this case came to necropsy and a colon measuring 82.4 cm. in circumference was found, a careful search of the literature was initiated. The following facts were gathered: Judd and Thompson

(1) in their report of 65 cases of megacolon stated that a megacolon of 70 cms. in circumference had been described. Formad (2) reported a case which contained 40 lbs. of feces and measured from 37.5 to 75 cm. in circumference. Yeomans (3) states that Hawkins had a case 108 cm. in circumference, but Hawkins' (4) original article clearly points out that this measurement was around the abdomen at the level of the umbilicus. Terrys' (5) unusually large case only

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Submitted April 15, 1940.



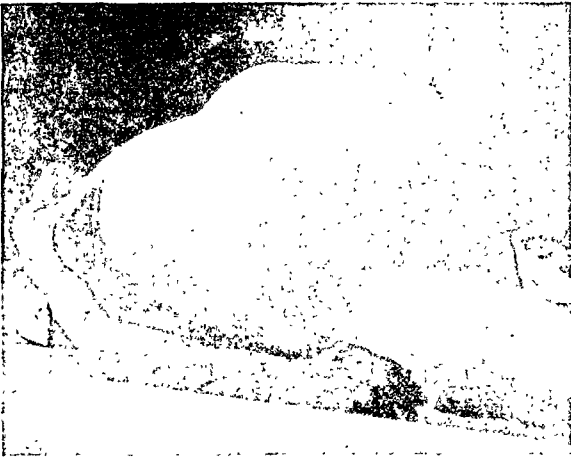


Fig. 1

measured 19 cms. in diameter (approximately 60 cm. in circumference) at its greatest point. Pinney found that up to 1908 only 206 cases of megacolon had been reported. At Cook County Hospital 7 cases were observed clinically from 1933 to 1938 and only 5 cases of megacolon were noted out of 21,341 autopsies performed from 1928 to 1939 inclusive. Of these, the largest measured 44 cm. in circumference.

#### CASE REPORT

W. K., a 27 year old white male, died enroute to Cook County Hospital. According to his mother, he had been troubled with abdominal swelling and constipation since the age of six months. This had always been relieved with enemas and mild cathartics. At the age of two months he had "pneumonia and brain fever," which left him mentally unbalanced. He often did peculiar things, laughed to himself and made queer noises. This continued on into adolescence, although at no time did he become violent or have fits. He was able to understand fairly well, but had great difficulty in talking. His mother noticed that he had strange and peculiar dietary habits, sometimes eating two to three pounds of bologna sausage at a time and stuffing himself with prunes. She often thought that he swallowed foreign bodies, but was never able to catch him doing it. Ten days before the fatal illness he complained of severe pains in the abdomen. These had come on rather gradually with an inability to move the

bowels. Abdominal distension occurred and became progressively larger. Attempts of all sorts were made to move the bowels, but with no success. Suddenly, without any warning, he passed a large quantity of blood from the rectum. This was estimated at two cupsfull. Following this he was brought to the hospital but died before admission.

Necropsy revealed a body of a slenderly built white male with a weight of 136 lbs. and a height of 152 cm. The musculature was atrophic, there was no edema and there were no signs of external violence. The abdomen was markedly distended and very tense. It was over a hands breadth above the level of the chest. The veins of the neck, chest and extremities were markedly distended.

The thoracic cavity showed the lungs markedly compressed and the diaphragm on both sides markedly elevated. The lower lobes of both lungs were sub-crepitant to non-crepitant. On sectioning, they were atelectatic and



Fig. 3

congested and there were focal areas of broncho pneumonia throughout. The heart weighed 250 gms. and was displaced upwards.

The mid-line fat was 1 cm. in thickness. On opening the abdominal cavity the intestinal loops instantly protruded due to the intra-abdominal pressure. The loops of the small intestine were moderately distended, whereas the colon was markedly distended with gas and feces. The large bowel measured 6.5 feet in length and weighed 45 lbs., when emptied it weighed 6 lbs. It measured up to 82.4 cm. in circumference (equivalent to 10.5 inches in diameter). An enormous, hard fecalith, measuring 11.5 x 10 x 9 cms. and weighing 535 gms. was present in the sigmoid. Above this mass were many foreign bodies, including twenty-five prune and peach pits, several pieces of corn cob, iron washers and a piece of iron approximately the size of a ten penny nail. At the site of the fecalith there was a large decubitus ulcer in the mucosa and throughout the sigmoid there were several small superficial ulcerations. The wall of the colon was firm and



Fig. 2

thickened. The liver weighed 1400 gms., was displaced to the right, flattened and compressed by the colon. It was soft and the markings were distinct. The appendix appeared unchanged. The spleen weighed 200 gms., was soft and pale in color. It was displaced upward. The stomach was slightly compressed and contained several hundred pieces of diced turnip. The kidneys, adrenals, pancreas and genito-urinary tract revealed no remarkable changes.

Microscopic section of the colon showed the mucosa intact, the capillaries congested and an increased amount of connective tissue in the submucosa. The muscularis was markedly hypertrophied and there was a moderate infiltration of round cells and polymorphonuclear leucocytes throughout.

A photograph of the huge megacolon and the enormous fecalith with the foreign bodies accompanies this report.

The literature reveals that most authors recognize two types of megacolon, namely, the infantile or congenital type and the pseudo-megacolon or the acquired type. The latter includes all those cases which develop after birth. Lockhart-Mummery (6) who collected from the literature, one hundred cases of megacolon, concluded on the basis of age incidence that most cases in adults were congenital and had been present since birth. However, the same author reported a case of acquired megacolon in a 54 year old adult who had

been perfectly well up to the age of 37. Shelley (7), Sagal (8), Scetta (9) and others report cases of acquired megacolon in the adult.

#### SUMMARY

Whether the megacolon in this patient was due to a congenital defect in the innervation of the colon and its sphincters, or to a defect in the innervation secondary to the "brain fever" suffered at two months of age is conjectural. However, it is quite probable that the mental deficiency associated with poor personal hygiene and pica was an important contributory cause of the megacolon in this case.

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## Recurrent Cholangitis Due to Common Duct Stone Associated With Colon Bacillus Infection\*

By

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and

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A WHITE woman, aged 54, not married, was first admitted to Bellevue Hospital on November 30, 1933, complaining of severe pain in the right upper quadrant of six days' duration. The pain was sudden in onset, colicky in character, and radiated to the back. It was aggravated by fatty foods, and relieved only by morphine sulphate hypodermatically. The pain was associated with nausea, vomiting, belching and distention. Persistent jaundice developed soon after onset of the pain. There had been no loss of weight. Except for a history of indigestion over a period of years, the patient had no other complaints. The patient was obese and acutely ill. The sclerae and skin were jaundiced. The temperature was 106, pulse 90, and respirations 22. The abdomen presented tenderness and rigidity in the right upper quadrant without a palpable mass. The urinalysis was negative. The white cell count was 14,000, polys 88%. A diagnosis of acute cholecystitis was made and operation was performed on the day of admission. At operation the gall bladder was found to be acutely inflamed, and it contained stones. The operative procedure was limited to cholecystostomy since the patient's condition was

so serious. Culture of the gall bladder bile yielded *B. coli* and streptococcus viridans. Convalescence was uneventful. The patient was discharged 21 days after operation, improved.

Three and one-half months later (April 11, 1934) the patient was readmitted complaining of abdominal pain of 32 hours' duration. The pain began suddenly, was located in the epigastrium and the right upper quadrant, radiated to the back and was associated with nausea, belching, distention, but no chills or jaundice. Examination revealed her temperature to be 101.8, pulse 72, respirations 20. There was no evidence of clinical jaundice. There was tenderness in the right upper quadrant and the liver edge was palpated four fingers below the costal margin. The white cell count was 18,000, polys 78%. A pre-operative diagnosis of acute cholecystitis was made and cholecystectomy was performed on the day of admission. At operation the gall bladder was found to be acutely inflamed with a stone in the cystic duct. The operative report also described the presence of large glands along the common duct. Culture of the gall bladder bile revealed *B. coli*; the gall bladder wall showed *B. coli* and staphylococcus aureus on culture. The patient's convalescence was complicated by a

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biliary fistula. She was discharged from the hospital on her 25th post-operative day, improved.

Two months later (June 9, 1934) the patient was admitted again complaining of epigastric pain of two days' duration. The pain was located entirely in the epigastrium, colicky in character, sudden in onset, radiated to the back and was associated with nausea, vomiting, belching, distention, fever and chills. The temperature on admission was 104.2, pulse 96, respirations 20. The sclerae were slightly jaundiced. There was tenderness in the epigastrium but no rigidity or mass. A diagnosis of obstructed biliary fistula was made and the obstruction was readily removed by means of a small incision in the skin at the point of tenderness. The patient's temperature immediately dropped to normal and the jaundice subsided. The patient was discharged, improved, 12 days after admission with a draining biliary fistula.

Three and one-half months later (September 21, 1934) the patient was readmitted complaining of pain in the right upper quadrant and fever of one day's duration. The pain and fever were associated with soreness in the right upper quadrant and a persistent biliary fistula. Examination revealed the temperature to be 101.7, pulse 80, and respirations 20. Clinical jaundice was present, the right upper quadrant presented a fistula discharging bile. X-ray examination of the abdomen revealed no shadows of calculi in the right upper quadrant. The patient was observed at the hospital without operative intervention. The temperature dropped to normal three days after admission, remained normal for a week, then rose again for a day, following which it returned to normal and remained normal. The patient was discharged 17 days after admission with a discharging biliary fistula.

Sixteen months later (February 10, 1936) the patient was readmitted complaining of right upper quadrant and epigastric pain of a days' duration. The pain came on suddenly, was very severe, radiated to the back, was associated with nausea, vomiting, belching, distention, fever and chills. Jaundice appeared on the second day of the attack. On examination the temperature was 104, pulse 90, respirations 20. The patient was jaundiced. There was tenderness in the right upper quadrant without rigidity or mass. The biliary fistula was no longer discharging. White cell count was 21,800, polys 84%; red cell count was 3,800,000, hemoglobin 70%; icterus index was 60, the direct van den Bergh test was immediate, the indirect was positive; the bleeding time was 3 minutes, and the coagulation time was 9 minutes. Biliary drainage was performed in the Out Patient Department prior to onset of jaundice and revealed the presence of calcium bilirubinate pigment. Seven days after admission (February 17, 1936) the common duct was explored and numerous small stones were removed from both the common duct and hepatic duct. A catheter was inserted into the common duct for drainage. Culture of the common duct bile yielded *B. coli*. The patient was discharged, improved, wound healed, one month after admission.

Three years later (November 19, 1938) the patient was admitted again complaining of right upper quadrant pain of 13 hours' duration. The pain came on suddenly, was colicky in character, radiated to the back, was associated with belching, distention,

jaundice, clay colored stools, fever, chills, and tenderness in the right upper quadrant. The temperature was 105.4, pulse 100, respirations 20. The patient appeared jaundiced, the abdomen was negative except for the presence of operative scars. The white cell count was 9,000, polys 78%; the red cell count was 4,800,000, hemoglobin 90%; the blood cholesterol was 160; bleeding time was 1 $\frac{3}{4}$  minutes and coagulation time was 3 minutes. Six days after admission (11/25/38) the common duct was explored a second time. A stone the size of a pullet's egg was found in a dilated common duct. This stone was removed piecemeal and a T-tube inserted for drainage. Convalescence was complicated by wound infection and a fecal fistula. On the fifth post-operative day the T-tube came away spontaneously before it was possible to make a cholangiogram. The patient was discharged 44 days after operation, improved. The fecal fistula, however, persisted. X-rays taken following injection of lipiodol revealed communication of this fistula with the colon.

Six months later (June 29, 1939) the patient was readmitted complaining of persistent fecal fistula. It had been present since her last operation. The fecal fistula was not associated with any pain or discomfort. The patient had no fever or jaundice and there were no associated abdominal signs. Iodoform paste was injected into the fistula daily for a week with temporary cessation of discharge at the end of this time. However, the fecal discharge soon recurred and persisted until February 14, 1940, when the discharge ceased.

The patient was last seen on February 20, 1940, when she appeared jaundiced. At the time, she stated that six days previously she had had another attack of biliary colic with jaundice, fever, chills, nausea, vomiting, belching and distention. A sterile biliary drainage performed on February 14, 1940, revealed the presence of *B. coli* and streptococcus aureus in the bile obtained from the duodenum, as well as cholesterol crystals and calcium bilirubinate pigment. The gastric contents showed a free hydrochloric acid of 43.

#### DISCUSSION

This case is of interest illustrating recurrent cholangitis due to common duct stone, associated with colon bacillus infection. The patient repeatedly sought relief because of pain, fever and chills, associated with jaundice. At the first operation, because of the patient's poor general condition, the operative procedure was limited to cholecystostomy. At the second operation 7 months later, the gall bladder was removed. When the patient returned 2 months later, a diagnosis of common duct stone was made. Operation was postponed, however, because it was thought the patient could not tolerate common duct exploration. Three months later the patient returned with findings of jaundice again but these symptoms subsided after a few days. One and a half years later when the patient returned with the same symptoms it was decided to operate and many common duct stones were found and removed. Two years later a recurrence of symptoms necessitated exploration of the common duct a second time. On this occasion a stone the size of a pullet's egg was found in the common duct. This was

removed piecemeal. This operation was complicated by a fecal fistula which ceased discharging just recently.

The patient still suffers with attacks of biliary colic, associated with symptoms of cholangitis. The presence of *B. coli* in the bile with cholesterol crystals and calcium bilirubinate pigment indicates the presence of common duct stone. The patient is obviously still a

surgical problem. It is impossible to predict whether another common duct exploration will result in a cure or whether this operation will have to be repeated again and again. The stones either reformed or were overlooked in the upper hepatic ducts where they were inaccessible. A cholangiogram would be an essential part of any future operative procedure on the common duct.

## IV. A New Test of Liver Function Determined from the Concentration of Bile Salts in Bile and Urine

### Studies of Liver Function in Health and Disease

By

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IT is generally conceded that currently employed liver function tests still leave much to be desired as an accurate index of the function of the liver. This is particularly true as to the need for a more sensitive and physiologic index of hepatic function and dysfunction—in contradistinction to our present tests for liver function which are more in the nature of gross or "pathologic yardsticks" of liver damage. Accordingly an investigation into the feasibility of estimating the bile salt concentration in bile was undertaken since it has been a repeatedly established fact of sixteen years standing that the bile salt concentration is the most sensitive index to the function of the liver in the experimental animal.

It was Smyth and Whipple in 1924 (1) who first demonstrated conclusively that when experimental animals were subjected to various hepatotoxins such as chloroform, carbon-tetrachloride, and tetrachlorethylene—amongst various functions of the liver the bile acid manufacture showed the earliest and most profound suppression. This was amply corroborated by subsequent investigators, particularly Bollman and Mann (2) in the animal, and in the human by Greene, Walters and Frederickson (3), by Ravdin, Johnston, Reigel and Wright (4), by Reinhold and Wilson (5), by McClure (6), by Adlersberg (7), by Minnibeck (8), by Grey, McGowan, Nettrours and Bollman (9) and by Morrison and Swalm (10-13) and others (14-18).

Since the time of Fourcroy in 1790 (19), constant attempts (20-26) have been made to isolate and quantitatively evaluate the various constituents of the bile, particularly the various bile salts. To date these have not been successful due to a variety of reasons. Some of these have been the lack of a specific quantitative method which has not been unusually intricate, elaborate, or prohibitive in cost of apparatus as is the

fluorescent spectrophotometer — which in addition must be especially designed and constructed.

In view of the present impossibility of isolating all the individual bile salts, the author succeeded in developing a stalagmometric method for estimating the total bile salt concentration in bile and urine. The total bile salts were estimated since Sabotka (27), Doubilet and Colp (16), and others have shown that under pathologic conditions the individual bile salts may undergo wide variations. The stalagmometric method employed by the author has been described in three previous publications (10-12) as being the most desirable method available at present since it is: (a) simple to perform, (b) inexpensive, (c) is not time consuming, requiring approximately twelve minutes to do, (d) needs no training, (e) is the most sensitive and accurate available test for the total bile salts present, and (f) is practical for everyday use. For the sake of clarity a summary is repeated here.

#### METHOD

The most outstanding physical characteristic of the bile salts is their surface tension activity. Doumer's law (28-29) states that when bile salts are added to a watery solution, the concentration of the bile salts varies inversely with the surface tension of the liquid. This holds for solutions of a dilution of 1 : 1000. However, when other electrolytic substances are added to this solution, the surface tension of the liquid varies according to the Schulz-Hardy Law. Then the surface tension of the liquid no longer reflects the bile salt concentration.

However, when a pH of 2 in the solution was maintained it was shown by Duco and Panza (26) that only the bile salts were active so far as the surface tension was concerned. Hence, by keeping the bile and urine at a pH of 2 it is possible to estimate the concentration of total bile salts in bile or urine, provided a dilution of 1 : 1000 is kept. As described previously (10-13) the surface tension of known concentration of bile salts in many and varying dilutions was estimated and charted as a curve in the graph which is shown.

For the estimation of the bile, 10 ccs. of a representative specimen of "C" or liver bile, "B" gall

From Temple University Medical School and Hospital, Department of Medicine, Pennsylvania Hospital and the Doctors' Hospital. Particular appreciation is extended to Dr. Robert H. Hamilton, Jr., of the Chemistry Department, Temple, for his unstinting aid and advice. Grateful acknowledgment is made to Drs. William A. Swalm, William N. Parkinson, Charles L. Brown, and the surgical services at Temple for cooperation in these studies; and to Drs. Leon Herman and William J. Ezickson of the Pennsylvania Hospital.

bladder bile, or "BC," the combination of both from the Lyon non-surgical biliary drainage is measured off. This is then diluted ten times with distilled water. Concentrated hydrochloric acid is added drop by drop until the indicator Tropilene 00 changes from yellow to pink, at which point a pH of 2 is present. It is most practical to dip ordinary filter paper in the indicator, cut off a narrow strip and dip this in the bile solution as the acid is added. The bile solution is aspirated into the stalagmometer and the drops are allowed to run out at a starting rate of thirty per minute. The number of fallen drops is then compared with the standardized graph for that stalagmometer and the total bile salt concentration is immediately seen by the curve. The stalagmometer shown in Fig. 1 was made from an ordinary pipette with a capillary tube fused to one end and a sphygmomanometer "needle valve" placed on top to regulate more easily the flow of the drops. Biles and urines should be examined at ordinary room temperature (70 degrees F.). If an estimation is desired on a following day, the specimen should be stored in the refrigerator until desired, and then allowed to stand or be warmed to room temperature.

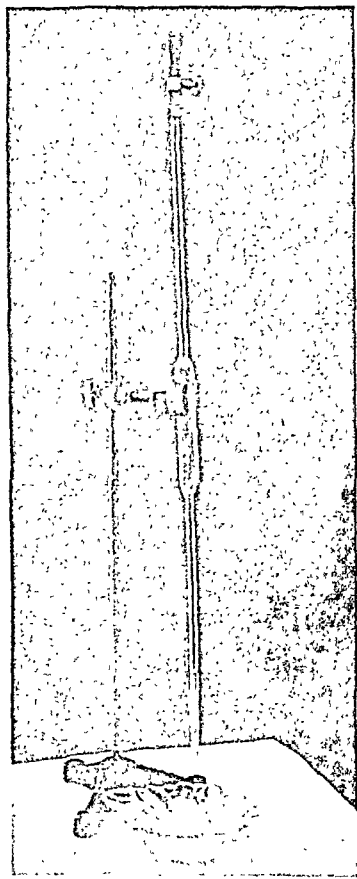


Fig. 1. Stalagmometer of the author with needle-valve attachment to regulate the rate of drops falling. The instrument shown was made from a 15 cc. pipette. The stalagmometer measures most accurately the surface tension of a liquid by the number of drops falling from it. (Made by Precision Thermometer and Instrument Co., 1434 Brandywine St., Philadelphia).



Fig. 2. Graph showing the curve of bile salt concentration in bile, obtained with the stalagmometer shown in Fig. 1. An unknown bile solution gives the number of drops read on the ordinate; from this the quantity of bile salts is seen immediately on the abscissa.

Fig. 2. Graph showing the curve of bile salt concentration in bile, obtained with the stalagmometer shown in Fig. 1. An unknown bile solution gives the number of drops read on the ordinate; from this the quantity of bile salts is seen immediately on the abscissa.

#### BILE SALT CONCENTRATION IN SURGICAL DRAINAGE BILE FROM PATIENTS WITH PATHOLOGIC LIVERS

The bile salt concentration from surgical drainage bile has been described previously (12) in considerable detail. A recapitulation of the findings follows:

The surgical drainage bile from diseased livers was found to reach a maximal post operative average of 740 mg. bile salts per 100 ccs. of bile. This was verified by a series of seventeen pathologic cases in which the patient's livers were inspected, palpated, and in a number of cases either biopsied at the operating table or autopsied. Daily estimations of the bile salt concentration in the surgical drainage bile were made from the beginning of drainage to the day the drainage tube was removed. It was observed that the bile salt concentration rose each day after the operation until a maximum was attained. As mentioned above, this maximum averaged 740 mg. per 100 ccs. for bile from the seventeen pathologic livers studied. However, in two cases of what was considered by the surgeon as macroscopic hepatic disease, the bile salts were concentrated within normal limits. It may be that the surgeon was mistaken in his estimate of the condition of the liver in these two questionable cases.

As the pathologist, Konzelman (30) has pointed out, our present pathologic methods are inadequate when estimating the functional impairment of the liver and certain other organs, by pathologically structural alterations in these organs, at autopsy or by biopsy. Thus, the deranged physiology of the liver during life may be at complete variance with the post-mortem findings in the pathological liver. Hence, an accurate portrayal of the true function of the liver during life is frequently not obtained from the disease seen at the autopsy table.

#### BILE SALT CONCENTRATION IN SURGICALLY DRAINING BILE FROM PATIENTS WITH NORMAL LIVERS

As was described in the previously mentioned surgical publication (12) thirty patients with normal livers proven at the operating table were studied. In these patients the daily post-operative surgical drainage bile was examined for the bile salt concentration, from the first post-operative day to the last day of

drainage. It was then found that the normal liver reaches a maximal concentrating power for bile salts which averaged 1800 mg. bile salts in the thirty patients studied. On an average it required a maximum of ten days post-operatively for the normal liver to reach this figure of 1800 mg. bile salts.

It was also then noted that there was a marked difference in the recuperative power of the liver

In these specimens care must be taken to permit the various stimulating solutions such as magnesium sulfate, peptone, olive oil, etc., to drain into a "discard" bottle, after they have been injected into the duodenal drainage tube. Thus, inadvertent dilution of the bile by non-body fluids is avoided to the necessary extent required for this method.

The "AC" bile, or bile directly from the normal functioning liver and bile ducts was found to range from 500 mg. bile salts per 100 ccs. to 1400 mg. although the average normal figure tended to center about the 600 mg. mark. The "B" bile or gall bladder fraction bile is increased in bile salt concentration from 1200 mg. to over 2000 mg. The minimal normal figure did not fall below 1200 mg. in this series. This was found to be a sensitive and accurate index to the function of the gall bladder, which normally concentrates the bile and bile salts. This study is the subject of a subsequent report (13).

The minimal low range limit for the combined "A," "B" and "C" bile was found to fall to 1200 mg. bile salts per 100 ccs. bile. Limitations of space prohibit the detailed analysis of this index of liver function, as compared to a large series of cases in which other currently used liver functional tests were studied and compared with the bile salt concentration. This is described in a separate communication.

#### BILE SALT CONCENTRATION IN NON-SURGICAL BILIARY DRAINAGE FROM PATIENTS WITH POORLY FUNCTIONING OR PATHOLOGICAL LIVERS

In a proven series of patients with abnormal liver function, who were or were not jaundiced, it was

Fig. 3. Graph showing the curve of undiluted bile salt concentration in the urine. This curve is the broadened duplicate (undiluted) of the first portion of the curve in Fig. 5 from the bile salt concentration in bile. In this way, the smaller and finer gradations of the bile salts in the urine are apparent.

following spinal anesthesia as contrasted with ether inhalation anesthesia. With ether the liver took practically twice as long to recover from the post-anesthetic "shock" as reflected by the greater and more prolonged suppression of the bile salts in the bile, and in certain cases, in the urine as well.

#### BILE SALT CONCENTRATION IN NON-SURGICAL BILE DRAINAGE FROM CASES WITH NORMAL LIVERS

During the past four years approximately 5000 bile specimens have been studied and as far as possible correlated with the clinical syndrome and clinical course, as well as with the currently used liver function tests such as the bromsulphthalein, the urobilinogen, galactose tolerance, hippuric acid, Van den Bergh, and the icteric index. In a number of these cases during this four year interval the patients were followed to the operating table or autopsy room for pathologic confirmation of the situation in the liver. In a small group of cases peritoneoscopy was performed by Dr. James N. Coombs, in order to visualize the liver.

It was found that the normal liver concentrates an average of 1500 mg. of bile salts in the combination of the liver and gall bladder biles known as the "BC" fractions.

The Lyon bile terminology of descriptive letters is meant here, as followed routinely where non-surgical biliary drainage is employed. "C" bile is the bile flowing directly from the liver, which is golden yellow in appearance, "B" bile is the concentrated bile from the gall bladder, being blackish-brown in appearance. "A" bile is the bile from the common and hepatic ducts and is a paler yellow than the "C" bile.

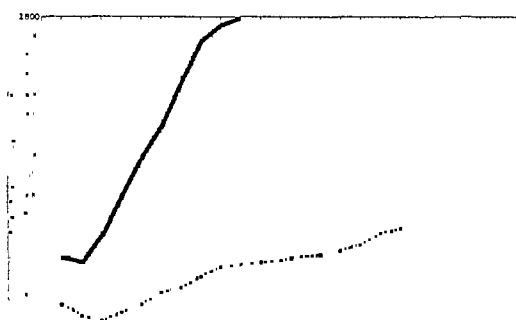


Fig. 4. Graph shows the average post-operative rise in the bile salt concentration of the surgical drainage bile from 50 cases with surgically proven normal and pathological livers. The maximal average for normal livers is seen to be 1800 mg. on the 10th day; that from pathological livers is seen to reach 740 mg. on the 18th day.

— Bile salt concentration in normal liver surgical drainage  
..... Bile salt concentration in pathological surgical drainage bile.

demonstrated that the bile salt concentration fell definitely below the levels just described above. That is to say, the poorly functioning liver shows a definite drop in the ability to concentrate bile salts. Since Bollman and Mann (33) were among the first to prove that the liver is the sole organ of the body to be concerned in the manufacture of the bile salts, it thus

becomes apparent that the bile salt concentration in the bile is a most sensitive index to the function of the liver. This is particularly true since McGowan (32), and Bollman and Mann (33) also revealed the unique sensitivity by suppression of the bile salt manufacture in the liver to noxious agents as chloroform, toluylenediamine, etc.

It was thus noted that in every jaundiced patient studied, with one exception, where bile could be obtained, there was a marked diminution in the concentration of the bile salts in the bile. This one exception was in the case of a hemolytic jaundice of unknown etiology, as reported elsewhere (34). In the early stage of this patient's disease probably no liver damage was present, and this was reflected in the normal bile salt concentration in the bile. It was always above 1200 mg. in the first week of hospitalization. However, in all other poorly functioning or

suppression in the bile salts would occur. These would most frequently fall in the "sub-clinical" range of 800 to 1200 mg. bile salts for the combined biles. Upon the treatment or removal of the underlying or causative factor, a rise into the normal range above 1200 mg. would regularly be seen. Although the patients were without symptoms, the presence of an icteroid tinge to the ocular sclerae was frequently observed.

It was this group, particularly, which proved of great clinical interest and significance. For here was seen no evidence of gross or clinical liver damage or dysfunction, and no abnormality with the usual liver function tests, and yet, when appropriate therapeutic measures were applied, the "latent" dysfunction disappeared with the coming of clinical improvement. There would then occur a rise from the grade one dysfunction with a subnormal figure of perhaps 900 mg. to a normal one of perhaps 1300 mg.

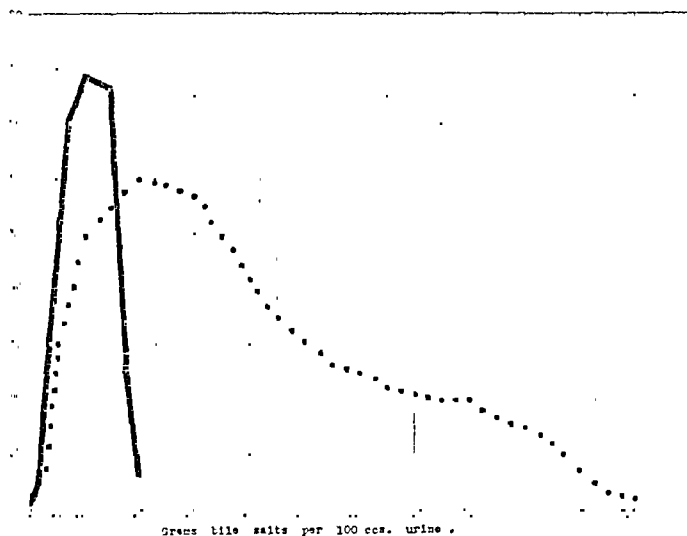


Fig. 5. Graph shows the distribution of the bile salt concentration in urines from cases with and without known liver disease, particularly in the presence of jaundice, as selected from over 5000 specimens. It is seen that the urinary bile salt concentration may rise to as high as 2.2 grams, in heavily jaundiced patients with hepatitis.

———— Bile salt concentration in urine from cases with normally functioning livers.  
 ••••• Bile salt concentration in urine from cases with poorly functioning or pathological livers.

pathologic livers the bile salt concentration usually dropped to from 100 to 800 mg. per 100 ccs. of bile in the combined "BC" bile fractions.

It may be stated here, however, that in every instance where the less sensitive tests of liver function showed some failure, the bile salt concentration test always showed a definite drop below the 1200 mg. level in the "combined" bile fractions.

But, further, the bile salt concentration test showed mild but definite suppressions or drops in concentration in the presence of such factors as great emotional excitement, vomiting of pregnancy (a group of thirty-five pregnant patients were studied before term), avitaminotic states, marked malnutrition, presence of extrahepatic disease as duodenal ulcer or extensive gastric carcinoma, or administration of sulfanilamide in heavy dosage. Under these conditions it was most frequently noted that a symptomless

It is believed from these observations that the bile salt concentration test is one of the most valuable liver function tests available. The other currently used liver function tests seem to be more in the nature of gross indicators of structural damage in the liver parenchyma. In addition, these are indicators of disturbances in other systems as well, such as the reticulo-endothelial system, this being true of the Bromsulphthalein test.

#### BILE SALT CONCENTRATION IN URINE FROM PERSONS WITH NORMAL FUNCTIONING LIVERS

The urines studied were twenty-four hour specimens without preservative. The quantity was measured and an aliquot portion (approximately four ounces of this total was taken) so that a portion could be aspirated into the stalagmometer. Urine specimens

were kept in the refrigerator until tested for bile salt estimation, when not performed within 24 hours of the collection of the total urine.

The normal patients, that is, free from any hepatic, gastro-intestinal or systemic disease, were selected from all the wards and from private rooms in the hospital. They comprised afebrile patients without any history of gastro-intestinal disease. Studies on approximately 5000 normal specimens are thus included, collected during the past four years. In this group are included a large number of orthopedic cases with fractures mostly of a minor type, patients in hospital for various lesser surgical procedures as hemorrhoidectomy, hernia, minor surgical procedures, gynecologic "repair" operative procedures, neurologic and neurosurgical and ophthalmic patients.

limits. It is thus noted that daily concentration of bile salts of urines in health are small and remain within limits of normal.

It is noted from Fig. 5 that seventy-nine per cent of all these patients free from known liver or gastro-intestinal disturbance excreted from 75 mg. to 200 mg. of bile salts daily in their urines at some time during the studies. Eight per cent of the patients in this "normal" group excreted from 25 mg. to 75 mg. at varying periods. Occasionally the bile salts of normal patients dropped to ten mg. An additional seven per cent of normal cases excreted from 300 to 350 mg., and 6 per cent of normal patients showed an occasional rise to 400 mg.

The normal patients were studied daily in periods varying from three days to three months.

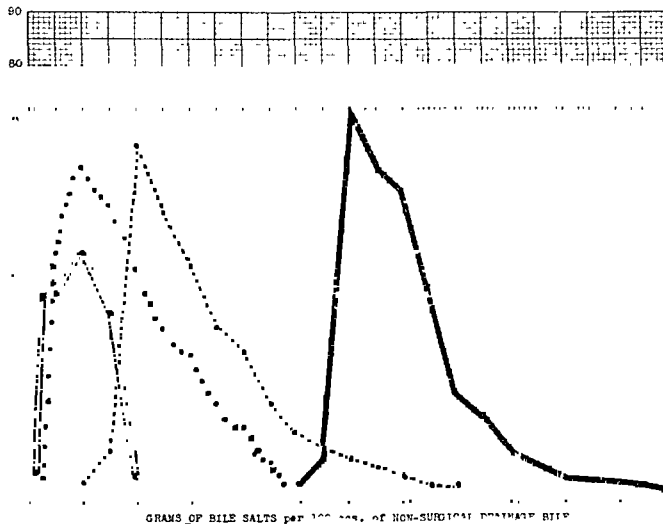


Fig. 6. Graph describes the bile salt concentration in non-surgical drainage bile (Lyon) from normal and pathological or dysfunctioning livers. Over 4000 biliary specimens are represented. It is noted that all but 6% of normal individuals have a bile salt concentration of 1100 mg. per 100 ccs. bile and above in the combined liver and gall bladder "(BC)" bile. Pathological or dysfunctioning livers fall definitely below this mark. Similarly the liver and duct "(AC)" bile normally concentrates bile salts to 400 mg. per 100 ccs. bile and above. Pathological or dysfunctioning livers fall below this level.

- Normal combined liver and gall "(BC)" bile.
- ..... Pathological or dysfunctioning combined "(BC)" bile.
- - - Normal liver and duct "(AC)" bile.
- - - Pathological or dysfunctioning "(AC)" bile.

It was found that in most cases, variations in the total daily urine output did not have a significant influence on the urinary bile salt concentration, although there were occasional instances in which a relationship did appear. For example, cases were found in which the total quantity of urine may have been doubled in one day, causing a small decrease in the total concentration of the bile salts. However, these variations always remained within normal limits and were apparently caused by markedly increased fluid intakes.

Similarly, the concentration of bile salts resulting from a diminished fluid intake and lessened urinary volume output, may cause a comparatively small increase in the bile salt concentration, but this again remains as a "borderline" variation within normal

## BILE SALT CONCENTRATION IN THE URINE IN LIVER DISEASE

It is seen from Fig. 5 that in jaundice, the bile salts may rise above the normal limit of 400 mg. to as high as 2800 mg. of bile salts in heavily jaundiced patients, especially those with an "intra-hepatic" type. In the jaundiced group of cases, intrahepatic (non-obstructive), extrahepatic (obstructive), and hemolytic types of jaundice were studied. As will be described in a subsequent communication, these three main and differing types of jaundice often fall into certain ranges of bile salt concentration in the early stages of jaundice. Hence, estimation of the bile salt concentration in the urine may prove to be an aid in recognizing the nature of a jaundice.



Generally speaking, it was found that in the early stages of the illness, cases of "obstructive" (extra-hepatic) jaundice, the bile salt concentration in the urine tended to stay within normal limits. This was true when there was no associated hepatitis or other liver disease to complicate the picture. It is thus apparent that the presence of complications with common duct obstruction, as by stone, can materially alter the data obtained from the bile salt concentration. The bile salt excretion thus tends to show the physiologic state of the liver, rather than what is happening in the ducts. This same criticism is true of other tests devised to help in making a differential diagnosis between obstructive and non-obstructive jaundice.

Patients with non-obstructive hepatitis were found to have bile salt excretion in the urine which rose above 350 mg. in the large series studied. This also included a group of hepatitis in which the liver disease was secondary to obstruction from common-bile duct stones, carcinoma of the gall bladder or head of the pancreas, or from post-operative common-bile stricture.

Included in this series was a considerable percentage of idiopathic hepatitis with so-called catarrhal jaundice. There were two subdivisions in this latter series, (a) those cases characterized by an afebrile course, and (b) those associated with fever of varying severity and a more or less pronounced toxicity. It was believed by some of the attending clinicians that the febrile cases in group (b) were of a different variety, possibly due to a virus or some infection. In any case, the bile salt excretion was definitely elevated above the 350 mg. level in all cases of group (a) and (b).

Three cases of hemolytic jaundice were studied extensively. One was of the "idiopathic" variety and two were cases of toxic reactions occurring during sulfanilamide therapy. In all three cases the bile salt concentration in the urine rose above normal limits, more than 350 mg. In the case of the "idiopathic" hemolytic icterus, a curious development in the course of illness ensued, as reported by Farrar, Burnett and Steigman (34) and an anoxic degeneration of the spleen and liver developed subsequently in the illness, as determined by surgical biopsy. In the early stages of the illness when the liver was not palpable and no gastro-intestinal symptoms were present, the bile salt concentration in the urine was always below the 350 mg. level. However, as the liver enlarged in size and was palpable, and a febrile and fulminating toxic clinical picture set in, the daily bile salt excretion rose above 350 mg. in the urine, and dropped to below 800 mg. in the non-surgical biliary drainage. The photomicrographs of the liver tissue were shown and reported elsewhere (34).

It is important to note here that many cases of low grade physiologic disturbances, reflected by impairment of the bile salt concentration in the bile showed a perfectly normal bile salt concentration or excretion in the urine. Similarly, there was a small group of

cases which were proven to have low grade but definite liver disease but which showed a normal bile salt excretion in the urine. These occurred in non-jaundiced patients and may be considered as instances in which the liver reserve and compensation were apparently still good.

The bile salt concentration in the bile of these cases was usually depressed in the "subclinical" range between 800 and 1200 mg. bile salts of the combined bile in the non-surgical biliary drainage, despite the normal bile salt excretion of less than 350 mg. in the urine.

The bile salt excretion in the urine has thus proved a useful check on the functional reserve or compensation of the liver where there was evidence of liver dysfunction by a suppression of the bile salt concentration in the bile.

#### SUMMARY

1. The bile salt concentration in the bile obtained by surgical and non-surgical drainage and urine from patients with normal and with diseased or poorly functioning livers was studied by a surface tension method employing a stalagmometer.

2. The bile salt concentration in the bile obtained by surgical and non-surgical biliary drainage is believed to be a most sensitive physiologic index to the function of the liver in health and disease.

3. (a) The bile salt concentration in surgical drainage bile from normal livers was found to average 1800 mg. per 100 ccs. bile.

(b) The same concentration in surgical drainage bile from a series of patients with pathologic livers has been found to average 740 mg.

4. (a) The concentration in representative non-surgical drainage bile from patients with normal livers was found to have an average normal figure of 1200 mg. This was taken from the combined gall bladder "(B)" and liver "(C)" biles, although figures above 1200 mg. were often obtained.

(b) Diseased or poorly functioning livers had an impairment in the power to concentrate bile salts, with an average of 800 mg. in the combined "(BC)" biles.

(c) The normal bile salt concentration from liver or "C" bile in the non-surgical bile drainage was found to be 400 mg. and over. The pathologic or dysfunctioning liver showed impaired concentrating ability, falling below 400 mg.

5. (a) The bile salt concentration in the urines of persons free from liver disease or dysfunction varied from 10 mg. to 350 mg. per 100 ccs. urine. There may be an isolated sporadic rise in the normal up to 400 mg.

(b) The bile salt concentration in the urine of persons with liver disease or poor liver function was often above 400 mg. per 100 cc. urine. The bile salt excretion in urine is not as sensitive an index to liver disturbances as is the bile salt concentration in the bile obtained by surgical or non-surgical drainage. Not infrequently the urinary bile salts are normal in non-jaundiced patients with hepatic dysfunction.

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## Exocrine Pancreatic Secretion in the Fasting Dog\*

By

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SINCE the experiments of Claude Bernard (1) many investigators have questioned the existence of fasting pancreatic secretion in the dog. The Pavlov school (Babkin (2)) believed that such secretion was a pathological hypersecretion of the pancreas; other investigators (Bylina (3), Inlow (4), Ivy and Farrell (5), L. Dragstedt (6)) evidenced belief in the existence of a fasting secretion. Zucker, Newburger and Berg (7) *proved*, by using the "altercursive intubation" method of Elman and McCaughan (8), that such pancreatic secretion was not a hypersecretion since uninterrupted introduction of pancreatic juice intraduodenally *failed to diminish* the "continuous" flow of pancreatic juice in the fasting dog. Dragstedt, Montgomery and Ellis (9) devised a method for the collection of all of the pancreatic secretion. Using a modification of this method Harms, Van Prohaska and Dragstedt (10) reported continuous pancreatic secretion in animals surviving 4-6 weeks. Crittenden and Ivy (11) observed continuous secretion in eight "enterectomized" dogs. We (12) have noted "continuous" pancreatic secretion in dogs with Dragstedt and Inlow fistulae surviving 6 months.

W. N. Boldyreff (13) reported extensive observations on the relationship between gastro-intestinal motility and pancreatic secretion. Fasting dogs with Pavlov fistulae secreted pancreatic juice *only* during periods of gastric motor activity; periods of regular "periodic" activity and "rest" for the bowel and pancreas were noted. Babkin (14) presented evidence for this relationship although his protocols showed *some secretion* during "rest" periods. E. Boldyreff

(15) confirmed the researches of W. N. Boldyreff. In all of these experiments the *type* of gastric motility observed cannot be determined because poor recording methods were used.

These reports of "continuous" and "periodic" fasting pancreatic secretion have led us to conduct experiments to compare the secretion in dogs with different types of fistulae.

### METHODS

Pancreatic fistulae were prepared by the methods of Dragstedt, Inlow and Elman and McCaughan. Techniques for the preparation and care of Dragstedt and Inlow fistulae are described elsewhere (12). Elman and McCaughan fistulae (8) were prepared according to the method of these investigators. In all cases the major duct only was used for the fistula, the minor duct was undisturbed.

Dragstedt fistulae were prepared with a short duodenal pouch receiving the main pancreatic duct; the pouch secretions were led to the exterior by a stainless-steel cannula. Pancreatic juice and succus entericus from the duodenal pouch were collected in a rubber bag suspended beneath the dog's abdomen.

Inlow fistulae were made by transplanting the duodenum and adjacent pancreas subcutaneously in the right hypochondrium; the main pancreatic duct was sutured to the abdominal skin 4 weeks later. Pancreatic juice was collected *only* during observation periods by a glass cannula cemented into the duct with collodion.

Each Elman and McCaughan fistula was prepared by tying a glass cannula in the main pancreatic duct.

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Secretions were led to the exterior via hemocytometer tubing.

Observations on the drop-by-drop pancreatic secretion were conducted upon 32 dogs trained to lie quietly upon a padded table for 2-6 hours. The secretion was conducted through a modified Gibbs (16) drop recorder which delivered an average of 16 drops of pancreatic juice per cc. All such observations were conducted 24 hours post cibum. Determinations of the pH of pancreatic juice were made with the glass electrode; no attempt was made to prevent aëration of the juice. Proteolytic strength of the juice was estimated by formol titration; the "zymogen" juice was activated by enterokinase.

## RESULTS

### Secretion in Dragstedt Fistulae

Pancreatic juice, active proteolytically because of admixture of pouch succus entericus, usually appeared

"Spurts" of secretion, such as observed by Zucker (7), were infrequently observed although fluctuations from 0-30 drops per minute were sometimes noted. These sudden changes in the outflow of juice gave the impression that the flow of secretion was being altered by sudden contraction or relaxation of pancreatic ducts. Frequently periods of prolonged augmentation in the rate of outflow occurred; such augmentation lasted for periods of a few minutes to several hours, or might be absent throughout an entire 6 hour period.

### Secretion in Inflow Fistulae

This fistula was easily prepared by the 2 stage method and proved a most satisfactory one for obtaining pure pancreatic juice. Secretion appeared in these animals 1-4 days post-operatively; the pancreatic duct was sufficiently healed to begin introduction of the collecting-cannula 10-14 days later. The juice

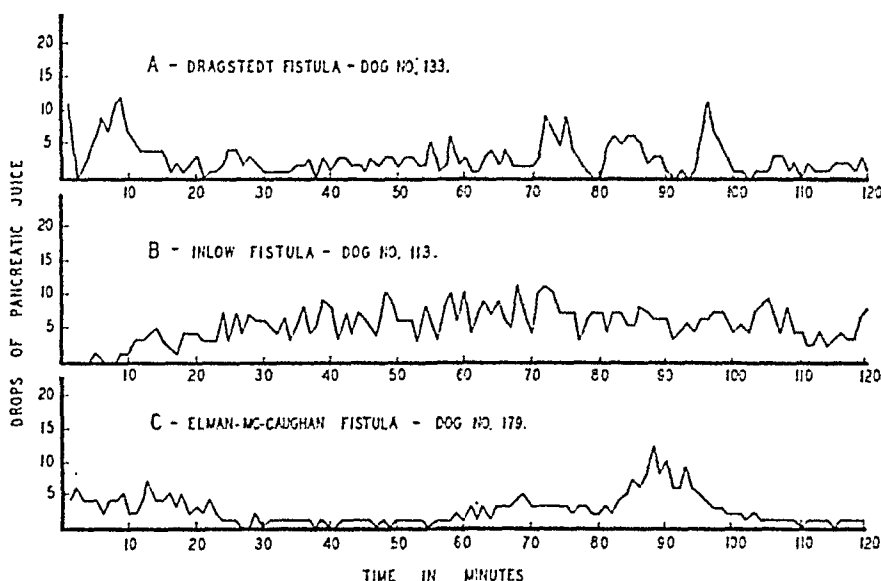


Fig. 1. Drop-by-drop pancreatic secretion observed, 24 hours post cibum, for a 2 hour period in the following: A, dog with Dragstedt fistula; B, dog with Inflow fistula; C, dog with Elman and McCaughan fistula.

24-72 hours post-operatively. This secretion was cloudy, abundant in quantity, and had a disagreeable odor. Examination of this juice showed the presence of abundant mucous-shreds and numerous bacteria. Fluctuations in the pH between 7.6 and 8.1 were noted.

These dogs secreted large quantities of pancreatic juice even during prolonged fasts; thus one 9 kgm. dog had a daily output of 250-515 cc. of juice during a 14 day fast.

The drop-by-drop secretion was recorded throughout 3-6 periods of 2-6 hours duration. Ten Dragstedt fistulae, under these conditions, averaged 1.49 cc. per kgm. per hour. No dog showed an "asecretory" period exceeding five minutes; generally these periods were much shorter even at very low secretory rates. Pancreatic outflow showed marked fluctuations in rate; Fig. 1A shows a typical result in which moderate fluctuations in the drop-by-drop outflow were recorded. In no instance was this outflow perfectly regular.

was clear, odorless, and contained neither mucous-shreds nor bacteria. This juice was proteolytically inactive, requiring enterokinase to activate its trypsinogen. The pH fluctuated between 7.02 and 8.80, with most determinations falling close to a mean of 8.3. This juice produced an "alkali dermatitis" in sensitive-skinned animals which required careful treatment (12).

Drop-by-drop fasting secretion was studied in 10 of these fistulae; the volume-flow from the transplanted duct in these animals averaged 1.55 cc. per kgm. per hour during the periods of observation. Outflow irregularities (see Fig. 1B) resembled those seen in Dragstedt fistulae but in contrast to the latter often showed an irregular periodicity, i.e., periods of outflow followed by "asecretory" periods occurring at irregular intervals. An occasional animal had no "asecretory" periods but "periodic" augmentation of outflow appeared at irregular intervals. Some of the fistulae had periods, sometimes lasting for days, of

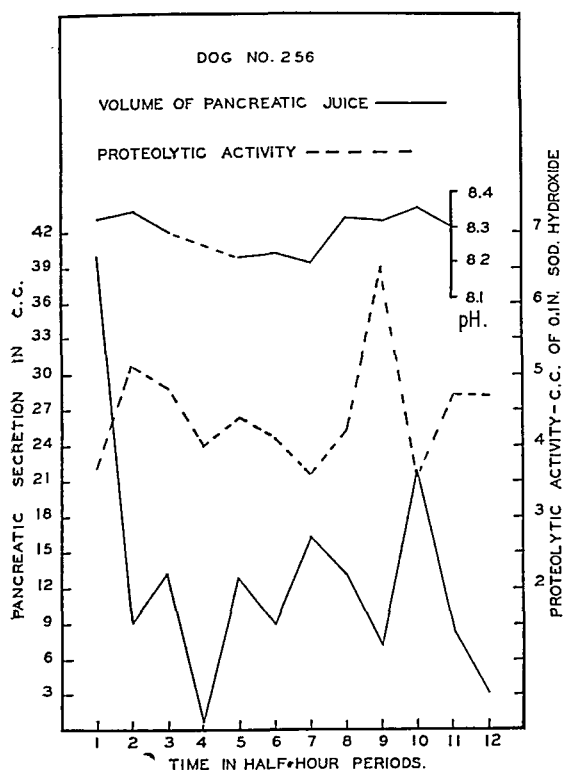


Fig. 2. Variations in the volume, pH, and proteolytic activity of pancreatic juice collected for 6 hours from a fasting dog with an Inlow fistula.

little or no pancreatic outflow which were followed by the reappearance of secretion. This finding, which has not been noted in Dragstedt fistulae, has not been thoroughly investigated. During the "asecretory" periods the duct orifice remained patent; deep catheterization of the duct did not secure pancreatic juice. Experiments (17) to be published in detail later, demonstrated that some of the augmentations in pancreatic flow were associated with gastric hunger contractions. Contrary to the findings of Boldyreff, our experiments proved that augmentation of secretion might occur *without* such motility.

Marked fluctuations in the secretory volume and proteolytic activity of fasting secretion occurred in these fistulae. Fig. 2 shows the results of one typical experiment. While the proteolytic strength of the juice was often inversely proportional to the secretory volume, this was not the rule (these observations confirmed Babkin (18)). The pH fluctuations in these experiments did not vary directly with the volume-flow of pancreatic juice.

Examination of the gastric content of gastrostomized dogs revealed that pancreatic secretory augmentations were not directly correlated with the presence of intragastric acid. Occasionally gastric juice (pH 1.0-1.5) was present in the stomach in quantities up to 200 cc. without initiating pancreatic secretion. We found no evidence of regurgitated feces, which had been noted by Elman and McCaughan in their experiments.

### Secretion in Elman and McCaughan Fistulae

The introduction of a glass cannula into the main pancreatic duct in this type of fistula led to many failures. The cannulae frequently pulled out and infections about the rubber drainage-tubes were difficult to prevent or combat. Occasionally a preparation survived for an extended period but this was, in our experience, the exception rather than the rule.

Under comparable conditions the secretory irregularities of these dogs resembled those seen in Inlow fistulae but the volume-flow of juice was smaller in the Elman and McCaughan fistulae. Fig. 1C demonstrates a typical experiment in which the irregular outflow showed two periods of augmentation. Although the volume-flow and drop-by-drop irregularities in these fistulae were of less magnitude than in Dragstedt and Inlow fistulae, only 6 such fistulae were studied thoroughly. These 6 dogs averaged 0.52 cc. per kgm. per hour during the periods of observation.

### What causes the irregularities in the fasting secretion?

One cannot observe the flow of pancreatic juice under the above conditions without being impressed by the irregularities in this flow. These irregularities have been observed in all fistulae studied but were smaller in the Elman and McCaughan type.

Anrep (19) observed that stimulation of the dog's

TABLE I  
Daily pancreatic secretion before and after intra-thoracic vagotomy

Day	Wt.	Fluid Intake cc.	Pancreatic Secretion	
			Total Volume	cc./Hr.
1	11.9	1000	405	1.43
2	11.1	1000	500	1.88
3	10.4	1000	400	1.61
4	11.0	1000	225	0.85
5	10.6	1500	550	2.12
6	10.8	700	450	1.73
7	10.8	850	675	2.60
8	11.6	850	700	2.52
9	10.6	450	560	2.19
10	10.2	1400	450	1.63
11	9.5	1800	410	1.79
Average	10.7	1050	484	1.85
12	Bilateral Vagotomy			
17	11.0	1000	500	1.89
18	11.2	1000	450	1.67
19	11.0	1000	335	1.23
20	11.7	1250	225	0.80
21	11.1	1000	280	1.04
22	11.1	550	225	0.95
23	11.4	1000	290	1.05
24	11.3	1000	340	1.25
25	11.3	900	250	0.92
26	11.5	1700	450	1.63
27	11.2	1400	425	1.58
Average	11.2	1072	342	1.27

vagus nerve constricted the pancreatic ducts, increased the volume of the gland, and inhibited the outflow of pancreatic juice. Korovitsky (20) demonstrated constriction of the pancreatic ducts, in the cat's pancreas perfused with Ringer's solution, when the vagus nerves were stimulated. Pilocarpine caused a highly irregular pancreatic flow which had been elicited by injecting HCl intraduodenally; these irregularities were attributed to irregular contractions of the pancreatic ducts.

In view of this evidence it seemed possible that vagotomy might abolish these variations in the outflow of pancreatic juice. To test this hypothesis the following experiments were conducted. Six Dragstedt fistulae were prepared and given daily 40 cc. of whole milk per kgm. and 20 gms. of dog biscuits per kgm. Water was allowed ad libitum and the daily output of pancreatic juice was recorded. Records were then obtained, under the conditions described above, of the

hour periods. It will be noted that the volumes are not appreciably changed by the vagotomies.

### DISCUSSION

Our results showed that the fasting pancreatic outflow in dogs with Dragstedt and Inlow fistulae was highly irregular, the latter often showed periodic "asecretory" periods occurring at irregular intervals, the former did not. The explanation of this difference is not obvious and will require further experiments. In Dragstedt fistulae the duodenal pouch received only pancreatic juice and succus entericus which might be responsible, in some way, for the absence of "asecretory" periods. Zucker (7) attributed the periodic outflow of juice in Pavlov fistulae (without evidence) to a differential resistance offered by the main and accessory pancreatic ducts. However, Dragstedt fistulae with patent accessory ducts did not show such periodic secretion. In Inlow fistulae, deep

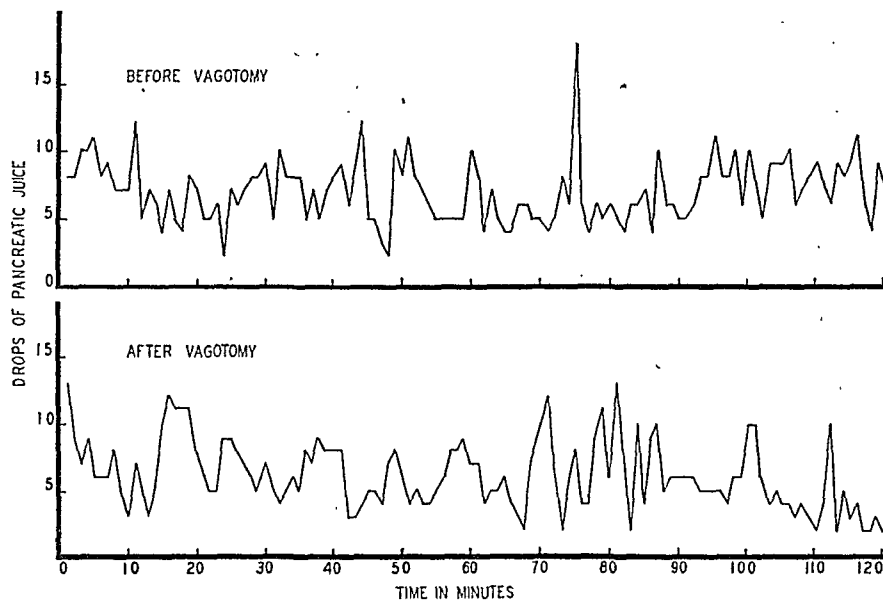


Fig. 3. Drop-by-drop outflow of pancreatic juice, in a fasting dog with a Dragstedt fistula, before and after bilateral intrathoracic vagotomy.

drop-by-drop fasting pancreatic secretion. After 3-6 observations on the rate of pancreatic secretion each dog received a bilateral intrathoracic vagotomy. Observations were then repeated on the drop-by-drop flow of pancreatic juice. Some of the observations after vagotomy were conducted as early as 72 hours post-operatively, others as late as 30 days thereafter. Fig. 3 shows the results obtained on one of the fistulae. These results were typical of all six animals. In no instance was there any reduction in the irregularity of pancreatic outflow following vagotomy.

The animals all showed considerable daily variation in the output of pancreatic juice before and after vagotomy. Table I shows a portion of such a record of one of these dogs. In this animal the average volume, per diem, fell slightly after vagotomy while in others the volume increased slightly. Vagotomy did not significantly alter the daily output in these animals. Table II summarizes the average fasting secretion obtained in these animals during the 2-6

catheterization of the ducts, during "asecretory" periods did not secure pancreatic juice. Experiments designed to answer this question directly must explain these discrepancies since the outflow of pancreatic juice should be similar in these fistulae because the accessory ducts were undisturbed and patent.

Our results proved that large quantities of pancreatic juice are secreted in a prolonged fast; this confirms Zucker (7) and Crittenden and Ivy (11). Since it is known that sham feeding elicits only a small volume of pancreatic juice (Crittenden and Ivy, Tonkisch (21), Scott (22)) it appears obvious that fasting pancreatic secretion cannot be attributed to conditioned reflexes.

While other explanations for the observed irregularities in pancreatic outflow are possible, the most acceptable hypothesis for such sudden changes is found in Anrep's (19) experiments which demonstrated that contractions of the pancreatic ducts often stopped the flow of pancreatic juice. If such contrac-

TABLE II

Average fasting secretion of pancreatic juice in Dragstedt fistulae before and after intrathoracic vagotomy

Dog No.	Secretion in cc. Per Kgm. Per Hour	
	Before Vagotomy	After Vagotomy
100	1.72	2.32
102	2.23	2.15
109	1.40	1.65
133	1.26	1.15
134	1.27	0.73
141	0.72	1.00
Average	1.43	1.50

tions (and subsequent relaxations) of the ducts accounted for the irregularities in outflow which we observed, it must be concluded that vagotomy did not abolish such activity. In one Dragstedt fistula neither vagotomy nor sympathectomy abolished nor even altered these irregularities in outflow. Ductular motility, independent of extrinsic nerves, could account for the above findings. It seems probable that marked variations in the drop-by-drop secretion may result from a number of mechanisms which have not been investigated; some of these are now being studied in

this laboratory. Irregularities in the outflow of pancreatic juice were essentially the same in the transplanted duct as in the duct which entered the intestine. In Elman and McCaughan fistulae the secretory rates were lower and showed less irregularities from minute to minute. It is possible that these differences were the result of the irritation of the cannula employed in this fistula.

Our experiments showed that bilateral vagotomy did not reduce the volume of pancreatic juice collected from Dragstedt fistulae nor diminish the volume obtained 24 hours post cibum. This evidence suggests that the vagus nerves do not play a major role in controlling the volume of pancreatic juice.

## CONCLUSIONS

1. The outflow of pancreatic juice in fasting dogs with fistulae showed marked irregularities. These irregularities were greater in Dragstedt and Inlow than in the Elman and McCaughan fistulae.

2. Inlow and Elman and McCaughan fistulae often showed "asecretory" periods which were "periodic" at irregular intervals; Dragstedt fistulae did not show such periods.

3. Bilateral intrathoracic vagotomy did not alter the irregularities in pancreatic outflow of Dragstedt fistulae nor the volume of juice collected from these animals.

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## A New Nasal Duodenal Tube\*

By

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A NEW nasal weighted duodenal tube is here described. It seems to have certain advantages over those now in use which, with the exception of the Levin tube, are introduced by mouth (e.g. Rehfuß, Einhorn, Twiss). It is made of soft latex rubber with the weight incorporated in the non-enlarged end. The tube is of the same diameter throughout. The weight is composed of small "bee-bee" lead shot. The end,

therefore, allows of bending and can be easily passed through the posterior nares.

A nasal tube has great advantages over mouth tubes in that the majority of patients rebel, either consciously or unconsciously, at swallowing. Moses Einhorn has made a successful effort to overcome this fear by encasing the metal tip in rubber which keeps it out of sight. It must, nevertheless, still be swallowed. In many instances the effort of swallowing will pro-

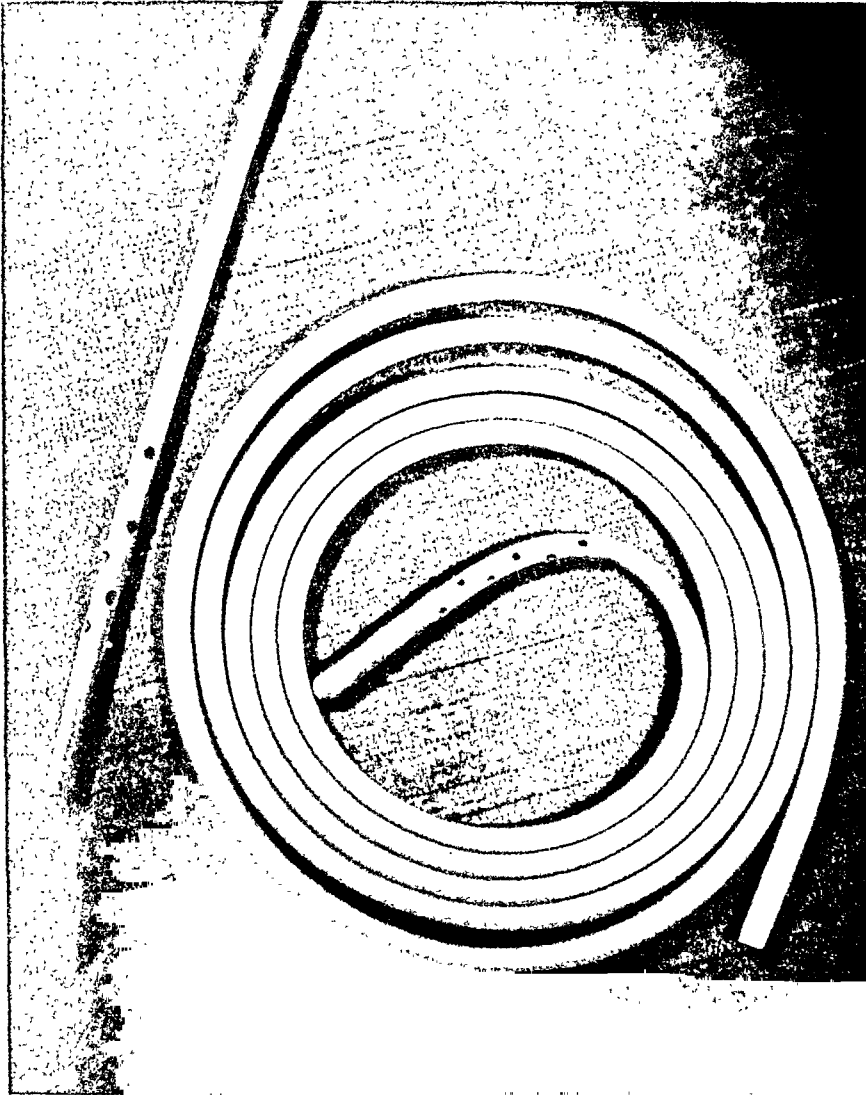
\*Manufactured by American Anode Company, Inc., Akron, Ohio.  
Submitted May 9, 1940.

duce a reflex pylorospasm. This results from either the pharyngeal irritation produced by, and at the curve in the tube, or from the gagging. This is in reality the first act of vomiting (reverse peristalsis) and is a definite hindrance to the tube entering the duodenum. There is little or no pharyngeal irritation with a nasal tube and fear is greatly lessened.

The soft rubber prevents irritation at any point of contact so that the incidence of probable esophageal irritation, or even ulcers, is greatly diminished and discomfort is practically absent. The thin walls do not allow of much suction before they collapse and because of this the mucous membrane is less likely to

be traumatized by syringe suction. Therefore if blood is present in the drainage it can be assumed that it is not the result of "suction trauma."

Lake has recently shown that the heavier weights do not appreciably hasten the entrance time into the duodenum and also that the Levin tube with no weight takes the longest time. The weight of this tip is not as much as the ordinary ones but is more than the weightless Levin. It combines the advantages of a nasal tube and a weighted tube. This tube—in a short experience—passes into the duodenum with less effort, and in a shorter time than either the Levin type or those which must be swallowed.



## A Biopsy Forceps for the Flexible Gastroscope\*

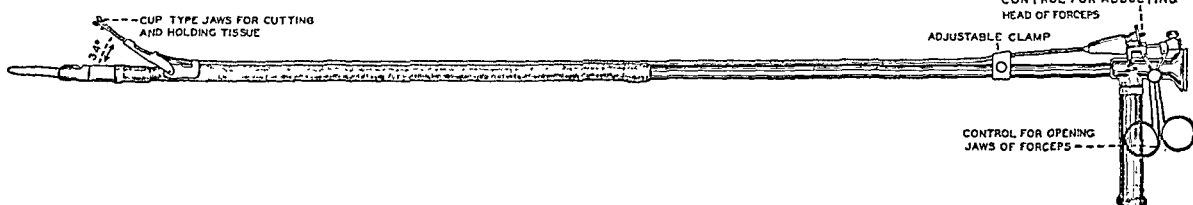
By

BRUCE KENAMORE, M.D.  
ST. LOUIS, MISSOURI

**T**HE desirability of taking a biopsy of the stomach under visual control with the Schindler flexible gastroscope should be apparent to anyone doing gastroscopy. The accompanying Fig. 1 illustrates a forceps attachment for this purpose. The instrument may be attached securely to the gastroscope and removed when desired. It is so constructed that there is no interference with the air channel of the scope. The maximum diameter of the forceps is 3 mm. The flexible gastroscope has a maximum diameter of 11

maneuvering the head can be brought into contact with gastric mucosa. The jaws are then opened and closed, biting off and holding a small piece of tissue. The head can then be adducted to the gastroscope, after which the whole is removed.

The forceps has been successfully used in taking biopsies from patients with carcinoma, atrophic gastritis, superficial gastritis and normal mucosa. There has been only minimal bleeding noted at site of removal of biopsy. The depth of bite of the forceps is



mm. which makes the total 14 mm. This does not approach the normal limits of transverse esophageal luminal width. Thus, if the gastroscope is introduced, with the attached forceps, the risk of trauma during introduction is not increased.

The head of the forceps lies directly over the objective and partially obscures visualization until it is elevated toward the stomach wall by the abduction of the distal 6 cms. of the apparatus. This action is controlled by a screw at the proximal end. With slight

too shallow to incur risk of perforation of the stomach wall.

The instrument can be employed effectively in any portion of the body of the stomach that is visible gastroscopically. It will reach as far as 1 to 2 cms. beyond the angulus into the antrum, but cannot be used for lesions adjacent to the pylorus. For lesions of the anterior wall in the pars media, over-distension by air inflation must be avoided to permit accessibility.

This procedure should be carried out only after a preliminary diagnostic gastroscopy has been done, and should be done by one experienced in gastroscopic technique.

From the Department of Medicine and Gastro-Intestinal Clinic, Washington University School of Medicine.

\*The instrument is made by the Phillips-Drucker Company of St. Louis, Mo.  
Submitted May 20, 1940.

## Editorials

### A NEW JOURNAL ON STUDIES ON ALCOHOL

**W**E welcome the appearance of a new magazine which will doubtless, in every number, contain much of interest to physicians. The name is the "Quarterly Journal of Studies on Alcohol." It is edited by a group of physiologists, psychiatrists and others interested in public health. It is published by Journal of Studies on Alcohol, Inc., 4 Hillhouse Avenue, New Haven, Connecticut, and the annual subscription is \$3.00. The first number is attractive and filled with material of much medical interest.

Of particular interest to gastro-enterologists is the article by Beazell and Ivy on the influence of alcohol on the digestive tract. After making a careful review of the literature they concluded that alcohol tends to

increase the output of acid more than the output of pepsin. Alcohol in concentrations greater than 10 or 15 per cent increases the secretion of mucus, probably because it irritates the stomach. It is probable that alcohol stimulates gastric secretion through causing the tissues to form or release histamine.

Alcohol in large amounts and high concentration causes acute gastritis with achlorhydria, from which recovery is fairly rapid. Chronic gastritis with achlorhydria can come with chronic alcoholism. It is not known how much of the gastric change is due to the alcohol and how much to an associated dietary deficiency. It is not known whether the gastritis predisposes to the formation of cancer of the stomach.

Alcohol obviously is not a good substance to give to patients with ulcer. The drug tends to inhibit hunger

Submitted September 11, 1940.



contractions. It may temporarily increase appetite by producing euphoria. Moderate amounts of alcohol have no consistent effect on the rate of emptying of the stomach, but 45 cc. taken with a barium meal may retard emptying. Alcohol slightly increases the secretion of pancreatic juice. In concentrations of from 5 to 10 per cent the drug inhibits the action of the digestive enzymes, but it is doubtful if such concentrations can be maintained for any length of time in the stomach. It has not been proved that alcohol in small concentrations will increase the amount of food consumed.

Alcohol is fairly rapidly absorbed from all portions of the alimentary tract. It is not absorbed so rapidly when taken with a meal as when put into an empty stomach.

Acute alcoholic intoxication depresses certain functions of the liver, but they recover from it rapidly. Abundant evidence indicates that alcohol alone does not cause cirrhosis of the liver, but it renders the liver more liable to injurious effects from other toxic substances.

W. C. A.

#### MULTIPLE CALCIFIED AREAS IN THE SPLEEN

**O**CCASIONALLY one will see in a roentgenogram many small areas of calcification scattered through the spleen, and then the question arises, what sort of disease could have produced the little nodules?

In most cases the history fails to throw light on what the disease could have been. According to von Orelli, writing in the *Deutsches Archiv für klinische Medizin* for December 21, 1938, in some of these cases the shadows are probably old healed tubercules, and he reported a few cases in which at necropsy microscopic examination of the lesions justified this diagnosis. He thought of three other possible explanations: one, that the shadows might be calcified animal parasites, second, phleboliths, and third, the remains of small granulomas. Unfortunately, even with the help of the microscope von Orelli could not always tell what the original lesion had been that became calcified.

W. C. A.

#### LATE RESULTS FOR THE TREATMENT OF DIVERTICULITIS

**I**N the London *Lancet* for December 17, 1938, Lockhart-Mummery analyzed the late results in the treatment of 136 patients with diverticulitis. Ninety-one patients were operated on, forty-five were not. Those that were not operated on were given liquid petrolatum to keep the stools soft. Most of these patients got along well, with only occasional mild attacks. Two died, one from sepsis and the other from peritonitis due to perforation of a diverticulum. These two patients had been advised to have an operation. In the whole series there were fifteen deaths attributable to diverticulitis.

In all the patients not operated on, the diverticula increased in size and number. This would indicate that the musculature of the colon continued to atrophy and become weakened.

In the thirteen cases in which operation consisted of freeing the colon and wrapping it in omentum, the results were excellent. In thirty-eight cases a colostomy was done using the transverse segment of the colon. Four of the patients in this group died; the re-

maining thirty-four who survived for long periods of time remained free from symptoms.

Lockhart-Mummery believes that colostomy is the safest and most satisfactory method for treating severe diverticulitis. In twelve patients the diverticula perforated into the bladder, producing a fistula. In seventeen cases the affected portion of the intestine was resected secondary to the performance of colostomy or cecostomy. Four of these patients died; the remaining thirteen recovered and had no further trouble.

The fact that seven of the patients developed severe arthritis, four endocarditis, and one each septic iritis, cerebral abscess and subacute combined degeneration of the cord suggests that infected diverticula can be a menace to the individual.

W. C. A.

#### CHEMICAL GRADIENTS IN THE BOWEL

**Y**EARs ago we prophesied that whenever research workers got around to measuring the concentration of various chemical constituents in samples of either mucous membrane or muscle removed at intervals of distance along the digestive tract, they would find a gradient with the figures ranging from large amounts in the duodenum or first portion of the jejunum down to small amounts in the terminal segment of ileum, and probably even to smaller amounts in the colon.

The first such chemical gradient discovered was in the catalase content of both the mucosal and the muscular coats. Schabadaseh found evidence of a gradient of pH in the nervous plexuses. Indications of other such gradients have been found, but they haven't been worked out in detail.

Now that it is known that acetylcholine has much to do with mediating the effects of nervous stimulation to smooth muscle, several papers by Gollart and Bacq are of considerable interest. They have shown in animals that there is a gradient in the acetylcholine content of the tissues of the intestine, ranging from high figures in the first portion of the jejunum to low figures in the colon. The figures for the esophagus and stomach were low. Interestingly, the amount of acetylcholine coming away from different parts of the intestine in the venous blood was also graded from jejunum to colon. As one might have expected, this gradient largely disappeared after the vagus nerves were cut and allowed to degenerate. Curiously, the flattening seemed to be due to an increase in the acetylcholine content of the lower part of the denervated bowel.

Just what these observations mean is as yet problematic, but every time such a chemical gradient is demonstrated, it seems more probable that there is an important connection between it and the obvious polarity of the bowel. There can be little question about the fact that every small section of the small bowel, at least from the first part of the jejunum to the neighborhood of the ileocecal sphincter, conducts better in the caudad than in the orad direction. Such a tube is said to be "polarized." Gradients of several types along the bowel can easily be demonstrated, and it seems probable that these associated gradients have something to do with the polarity. It would not be surprising if they accounted for it.

As Ross Harrison pointed out a few years ago, long, string-like protein molecules are probably arranged in

rows along the length of many primitive organisms, and the individual polarities of these long molecules probably add up to produce the easily demonstrated polarity of the organism. Here perhaps one gets a glimpse of the foundation stones and the beginnings of a biologic gradient. As Ross said, the head end of the animal is chemically different from the tail end, and there is a chemical and electric gradient ranging through the space between them.

As Child and his studies and others have shown again and again, the little area on the surface of a developing egg which happens to develop the fastest rate of metabolism becomes the embryo, and that end of the primitive streak which has the fastest rate of metabolism becomes the head end of this embryo. The growth of the animal longitudinally and laterally then follows along metabolic gradients that run out from the rapidly growing area.

W. C. A.

#### PATIENTS WHOSE CHIEF SYMPTOM IS DEPRESSION

**E**VERY gastro-enterologist could profit from reading the paper by L. H. Ziegler in the "Psychiatric Quarterly" for October, 1939, because so many of our patients come complaining primarily of having lost their "pep" and their enthusiasm, interest and joy in living. Often there are insomnia, loss of appetite and loss of weight. With this there go usually feelings of weakness and great fatigue. The patients feel sure they are being injured by poisons coming from some part of the body, and they insist that the physician locate and eliminate the source of this poison. Often the colon is blamed because when constipation is relieved the patient brightens for a few hours.

Faced with such a problem the clinician usually goes over the patient from head to foot, hunting for foci of infection or for a cancer or some other serious disease. Often the patient is put to great expense and annoyance; perhaps teeth and tonsils are removed, and removable organs, such as appendix, gall bladder, or uterus, if they happen to be at all diseased, are sacrificed.

As Ziegler says, while these things are being done, the really important fact about the illness usually escapes attention; namely, that the patient is entering a period of depression—really a mild melancholia due primarily to an inherited disease of the brain. Actually he or she should be in the hands of a psychiatrist and shouldn't be bothered and upset with operations and painful treatments. If a more careful history had been taken it would have been seen that the patient's main trouble was the depression, with the related loss of interests, perhaps feelings of guilt, and fear of insanity. Unfortunately, the distressing bodily sensations which accompany the disturbance in the brain and are probably secondary to it usually cause these patients to go to a clinician and not to a psychiatrist.

Unfortunately, in many cases such pressure is put on the physician to find something causative below the neck that in desperation he grasps at straws and begins treating the patient strenuously for such things as a slight hypotension or a slightly low basal metabolic rate or a slightly low blood sugar. Often a so-called mucous colitis is treated as the cause of the trouble when really it is only secondary to the depression. In most cases a talk with relatives would

have revealed the fact that the patient had always been a serious, self-centered, sensitive, and perhaps odd person who had worked hard without any hobby or avocation.

Unfortunately, when these patients seek medical advice, they will rarely, unless questioned closely, tell enough of their history to help the physician in making the correct diagnosis. They talk too little about the mental symptoms and too much about the peculiar and uncomfortable bodily sensations. Often the relatives are not helpful in bringing out the essentials of the history because they are so annoyed at the patient because of his "foolishness," his silly worrying, and his refusal to "snap out of it."

With the help of reassurance and sometimes occupational therapy, many of Ziegler's patients recovered. Of fifty-seven whose later history could be learned, four had grown worse and three were in asylums. Sixteen were no better, thirty were better, and seven appeared to be well. Forty-two were able somehow to keep at work.

As Ziegler says, one of the problems before the medical profession today is that of recognizing these depressions promptly and then treating the patient properly and intelligently. Obviously these people must not be scolded or exhorted to "snap out of it" because they can't snap out. Often they will be grateful when the physician explains the situation to the relatives and stops these Job's comforters from scolding and exhorting. Usually all that these patients need is good care for months or a year or two, and then they will slowly or suddenly come out of the depression without any outside help.

W. C. A.

#### THE DISCOVERER OF HYPOCHLORHYDRIA IN CASES OF CANCER OF THE STOMACH

**A** MAN whose name should be remembered and honored by gastro-enterologists is Golding Bird, one of the junior physicians working at Guy's Hospital in the years from 1843 to 1854. Unfortunately he piled more work on his frail body than it could stand and as a result he died at the age of thirty-nine. During his brief career he published many important papers, most of them showing signs of much originality.

He was one of the first to use a flexible stethoscope and to study its physical properties. Most interesting to us gastro-enterologists is the short series of papers published in 1841 and 1842 (1), in which he reported that a study of the vomitus of patients had shown that the amount of hydrochloric acid varied from day to day. He showed also that in normal persons filtered gastric juice was clear and watery, while in diseased persons, and particularly in persons with cancer of the stomach, it was often dark, due probably to the presence of some derivative of hemoglobin.

He showed also that in a patient who came in with a small carcinoma of the stomach obstructing the pylorus, hydrochloric acid was present in almost normal amounts. Later as the stomach became more diseased and the patient failed in health and strength, the amount of acid fell off and was replaced by organic acids. These conclusions were strengthened by a study of the vomitus of two other patients.

Unfortunately, as usually happens when a man is too far ahead of his time, these epoch-making papers

of Golding Bird received little comment, and as a result the medical world had to wait until 1879 when von den Velden, working with Kussmaul, showed that hydrochloric acid is commonly absent in the gastric juice of patients with advanced cancer of the stomach. Perhaps more attention would have been paid to Golding Bird's work if it hadn't been that he used a difficult and time-consuming technic for getting at the amount of acid in the vomitus.

A short biography of Golding Bird, with his bibliography, can be found in volume 76 of *Guy's Hospital Reports* for 1926. W. C. A.

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#### PIONEERS IN THE USE OF GAVAGE

THE student of medicine who cares to rummage around in old books will frequently be surprised at finding how old certain procedures are which he thinks were discovered recently. For instance, one reads in every textbook that the stomach pump was discovered by Kussmaul in 1869, but actually a review of the literature shows that stomach tubes and even the modern type of small tube was used long before. Avenzoar, the Arabian, was using stomach and rectal tubes about 1100 A.D.! A small tube was used in the United States by Dorsey and Physick about 1812 to save the life of a child who had swallowed laudanum.

Some time ago we got from Paris a little volume entitled, "Allaitement et hygiène des enfants nouveaux-nés," by Tarnier, Chantreuil and Budin. The first edition was published in 1882. On page 269 of the second edition, published in 1888, Tarnier writes that in 1851 Marchant published in the *Gazette médicale* of Paris a paper in which he proposed feeding marasmic infants through a small tube introduced through the esophagus. In 1861 Calorie in Bologna used this method for the feeding of a human monster. Reports of similar work were published by Fabbrie in 1865

Submitted September 19, 1940.

and 1870, by Belluzzi in 1874, and by St. Germain in 1884. St. Germain stated that in 1860 when he was an interne in the service of Legroux his chief taught him to feed weak children by gavage. Tarnier began using the method in 1884, and a Paris thesis was written on it in 1887 by Berthod. They used a urethral catheter.

Interesting is the paper of Scheltema, published in 1908, in which he stated that for years he had used the indwelling tube for gavage just as Tarnier had done. Scheltema apparently was one of the first to insist on the importance of fighting dehydration in infants suffering from diarrhea and vomiting. In order to keep children from vomiting the tube he passed it into the small bowel. He noted also that absorption of the food given was better when the end of the tube was in the small bowel. Occasionally he used the tube for sucking material out of the small bowel. Often he passed the tube through the nose.

Early in his work Scheltema passed a tube from nose to anus in a number of animals to make sure that this was safe, and he roentgenographed the tube to see how the coils of bowel were arranged.

W. C. A.

#### LETTER

#### PREVENTION OF POST-GASTROSCOPIC THROAT DISCOMFORT

IT is now well known that gastroscopy, when carried out properly, does not cause any serious discomfort and may be repeated many times if necessary. If the patient is very tense and is unable to relax satisfactorily, soreness of the throat may develop after the examination and persist from one to four days. We have recently found that the use of A-C Troches (Abbott) containing Anesthesin and Calcidin effectively prevents the development of this soreness. The Anesthesin, in particular, relieves the soreness almost instantly. We usually prescribe three of these tablets, to be sucked slowly during the twenty-four hour period after gastroscopy. Rudolf Schindler.

## Abstracts of Current Literature

FRANKLIN HOLLANDER, Associate Editor in charge of Abstracts, New York, N. Y.

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#### CLINICAL MEDICINE MOUTH AND ESOPHAGUS

LACASSAGNE, A.: Réactions de la glande sous-mammaire à l'hormone male, chez la souris et le rat. *Compt. Rend. Soc. Biol.*, 133:539, May, 1940.

Sex differences were found in the submaxillary gland of the mouse. In the normal adult male of 20 gm. weight the sub-maxillary and retro-lingual glands on one side together weigh 65 mg. in the male and 48 mg. in the female. The mean diameter of the tubules of the submaxillary in the sexually active male is 47  $\mu$  compared with 37  $\mu$  in the female. Castration or prolonged injection of estrogens in the male reduces both submaxillary gland weight as well

as tubule diameter. On the other hand, male sex hormone (testosterone propionate) increases both gland weight and tubule diameter to as much as 90 mg. and 60.5  $\mu$  respectively.

Although in the rat no sex differences exist with respect to the weight of the submaxillary, the behaviour of the gland towards male sex hormone is the same as in the mouse.—M. H. F. Friedman.

#### STOMACH

HANSMANN, S.: Tiefenschermerzkussion als Möglichkeit der genauen Schmerzlokalisation im Bereiche der

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